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EXPERIMENTAL INVESTIGATION
OF THE
ACTION OF MEDICINES.

PART I.
CIRCULATION.

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EXPERIMENTAL INVESTIGATION

OF THE

ACTION OF MEDICINES.

BY

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EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

PART I.

CIRCULATION.

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EXPERIMENTAL INVESTIGATION OF THE ACTION OF MEDICINES.

I.—The Standard of Health.

Modes of Investigation.—Pathology.—Pharmacology.—Life.—Conditions of Health and Disease.—Effect of Drugs.—Direct and Indirect Action.—Local and Remote Action.—Dose.—Modification of Dose.—Cumulative Action.—Effect of Habit, Climate, Fasting.—Form of Administration.—Effect of Large and Small Doses.—Homœopathy.—Constitution and Idiosyncrasy.—Explanation of these from Experiments on Animals.—Connection of Chemical Constitution and Physiological Action.

Gentlemen,—The usual mode of investigating the action of a remedy is to give it to a patient during an illness and observe what changes occur in the symptoms after its administration. But it not unfrequently happens that medicines are given without any distinct change in the symptoms ensuing; and, even when one does take place, we very often cannot be sure that it is due to the medicine, and not to the course of the disease or some other modifying cause. For, if the remedy and the disease are both at work together, it is obviously impossible for us to decide what part of the result is due to the one and what part to the other, if we neither know what the course of the disease would have been had the medicine been given, nor what action the medicine would have had if the disease had not been present. Any attempt to investigate the action of a remedy by giving it under such circumstances is like that of a rifleman to learn shooting by practising only at dusk, when he cannot see the butt, much less the bull's eye. He might go on practising for ever in this way without making any improvement; for, when he missed, he would never know whether it was because he had not seen the mark properly or had not aimed steadily at it. If he wish to learn, he must practise by daylight, when he can clearly see the mark, and can thus be sure that every miss is due to unsteady aim. He will fire high or low, to one side or the other, as he finds necessary, and, by gradually correcting every error, his aim will at last be sure. Should he then be called on to stand sentry on some dark night, and shoot at some suspicious object without hitting it, he would know that his failure was due to his not having seen the object distinctly, and having consequently aimed in a wrong direction. And just as the rifleman, before he stands sentry in the dark, must learn to shoot by daylight, when he can note the effect of each alteration in the position of his rifle on the course of the bullet, so ought we to investigate the action of our remedies in circumstances and under conditions which we know and can vary at will, marking the effect of each variation upon their action till we thoroughly and exactly understand what it is, before we proceed to give them in disease, when not only the conditions under which they operate are at present in a great measure unknown, but the effects they produce cannot be definitely ascertained from insufficient knowledge of what the result would have been had they been withheld. Of late years, it is true, vigorous efforts have been made to determine what course diseases run when not interfered with by medicines; and, although it is often difficult to say what the sequence of symptoms will be in any particular case, depending as it does not only on the general course of the disease, but on individual peculiarities of the patient and on the varying circumstances in which he is placed, we may nevertheless ascertain with tolerable accuracy whether or not our treatment is beneficial in a general way, even when we cannot determine its effects in detail.

Very inexact and very unsatisfactory as such a knowledge of medicines as this necessarily is, it must for the present be our guide in practice in a large number of instances; and our treatment at present and for some time to come will be chiefly empirical, because our knowledge of pharmacology, and perhaps still more of pathology, is not yet sufficiently advanced. For there is hardly any disease in which we know the exact nature of the morbid changes which are occurring, or the precise organs or tissues which are their seats; and, with some exceptions, we are but very imperfectly acquainted with the structures ou which our remedies act, and the exact mode in which these are affected by them. Day by day, however, our ignorance is diminishing; and we may hope that ere long rational treatment will to a great extent supersede blind empiricism. It not unfrequently happens at present that we meet with a case which bears a very close resemblance to others which we have treated successfully, and which nevertheless obstinately resists the remedies which we had previously found serviceable. Our failure astonishes and vexes us; but we are ignorant of its cause, and we can only select some other drug by guess and try it: we cannot at once choose the one which will have the desired effect.

PATHOLOGY.—In order to choose a drug which will have the effect that we desire to obtain, we must know where the morbid changes are taking place, and what their nature is; and we must be sure that our medicine will act on the affected part, and in such a way as to counteract the disease. We must trace every symptom which we see, back to its unseen source; every flush on the cheek, every quickening of the pulse, back to the vaso-motor or cardiac nerves, which have allowed the capillaries to become dilated, and thus produced the redness, or have permitted the heart to beat more rapidly than its wont. We must then inquire what has produced this alteration in the nervous system, and so on, till at last we discover, if possible, the hidden cause of the mischief. We will then give that remedy which will act in the proper way on the part which we believe to be the seat of the morbid process; and, if the expected result does not ensue, we shall, at any rate, have discovered what the pathology of the disease is not; and, by trying a remedy which will act in a different way or on a different structure, we may find out what it really is.

When I speak of the pathology of a disease, I do not mean those obvious alterations in the structure of an organ which we meet with in *post mortem* examinations, but the so-called functional changes which precede and are the cause of both them and the symptoms. For example, the disorganisation of a man's liver by the presence of an abscess, or of his kidneys by fatty degeneration, is not the disease from which he suffered, any more than a field strewn with slain or crowded with heaps of wounded is a battle. The disease was the alteration in the nervous and vascular systems, and in the nutrition of tissues, which we call the inflammatory process, and which produced the abscess and degeneration, and the disturbance of the same systems to which these lesions in their turn give rise; just as an army may not only lose the battle for want of the assistance which its slain and wounded would have given, but its retreat may be embarrassed by their presence.

The insufficiency of present modes of treatment, and the urgent necessity which exists for an accurate knowledge of pathology and pharmacology, are shown by the manner in which any new remedy is seized upon and applied in all sorts of cases, even in those where a knowledge of the morbid processes going on, and of the action of the remedy itself would at once have indicated that harm, and not benefit, must ensue from its application. It is unnecessary to discuss here the manner in which pathology must be studied in order that an accurate knowledge of it may be obtained: I may merely indicate as examples the works of Cohnheim, Brown-Séquard, Sanderson, Stockvis, Stricker, and many others.

PHARMACOLOGY.—In studying pharmacology, our first object is to find out on what structures a remedy acts. For this purpose, it is of no use to give it to a man either sick or well. We may do so in order to find out what general symptoms it produces; and from these symptoms we may guess at the structures affected; but, in order to convert our hypothesis into certainty, we must apply it to these structures or organs, and to them alone, and see whether the general result is the same; or we may prevent it from reaching them while it is applied to all other parts of the body, and observe whether the effect is absent. For this purpose, we cut off from one or other parts of the body the supply of blood which carries the drug along with it, or we may so injure the part that its function is abolished, and no action exerted upon it can produce any effect. But it is impossible to do this in man, and so we must have recourse to the lower anlmals, in which we can produce at will the conditions we desire. Although the administration of medicine to a patient is really an experiment, we vary the conditions in which it acts to so much greater extent in animals, that it is convenient to call the latter mode of investigation the *experimental method*, and the former that of *clinical observation*.

Now pathology and pharmacology may go on hand in hand both in teaching and study, but they must always be preceded by physiology; for, unless we know the processes which take place in the healthy organism, it is impossible to understand the changes they undergo in disease, or the effect of drugs upon them. I will, therefore, here say a few words regarding the processes in which life consists, before proceeding to speak of the mode in which they may be modified by the action of remedies.

LIFE.—We meet with life only in certain bodies composed of carbon combined in a very complicated manner with oxygen, hydrogen, and nitrogen; and it may, generally speaking, be said to be the power which these bodies possess of assimilating to themselves other substances, of decomposing them, and of evolving energy, which is shown in active motion, active growth, etc. Evolution of energy in this way is the distinguishing mark of life. When we look at a grain of wheat, an egg, or a dried wheel-animalcule, we are unable to say whether or not it is alive; it is only when it begins to evolve energy, either by moulding other substances into conformity with its own constitution in active growth, as in the seed or egg, or by active motion, as in the animalcule, that we are able to decide the question. We cannot say how these bodies originally came to possess their complicated constitution and wonderful powers; but the evolution of energy by which we recognise the continued presence of life seems to be more intimately associated with chemical affinity than with other forms of energy, such as light, heat, or electricity. All these forms of energy modify the processes which occur in living beings, both those which are chemical and those which we term vital, and apparently in much the same degree; but whether they modify the vital only through the chemical, we are at present unable to say. Instances may readily be found in which life continues active, although one or other of the forces mentioned is not supplied to the living body from without, and is only secondarily present as a result of chemical changes going on within. Thus a seed in the earth, a fungus in a cellar, or a proteus in its dark cave, live and thrive without a ray of light; and the whale and walrus in the Arctic seas are independent of any external heat, their temperature being only maintained by combustion taking place within their own bodies. But there seems to be no instance of vitality alone continuing active when a stop has been put to the occurrence of chemical changes. Sometimes both chemical and vital processes are suspended together for a time, as in a grain of wheat or a rotifer when it is kept dry, or in an egg when kept cool and coated with varnish to exclude air. So long as chemical activity remains dormant, no other form of energy can awake the latent vitality. Only when the conditions necessary for chemical transformation of the proper kind and amount are supplied, does it again become manifest. Thus light or heat may be applied in any amount or any proportion to an egg, a seed, or a dried rotifer, and still they will not grow or move if the air be withheld from the former or the moisture from the two latter, which is essential for the production of chemical changes within them.

CONDITIONS OF HEALTH AND DISEASE.—These changes of which I have been speaking consist in the assimilation of certain substances, their decomposition within the organism, and the rejection of waste products. A due proportion between these constitutes health. Just as a fire can only be kept bright by raking out the ashes and supplying fresh fuel as that in the grate burns away, so an organism can only be kept healthy by removing the products of waste and supplying fresh nutriment as its tissues get decomposed during action. The conditions necessary for this purpose are secured in the simplest forms of life, such as the amœba, by the little mass of protoplasm moving about in a fluid which can supply the oxygen to keep up combustion and evolve energy, and the nourishment necessary to replace the material thus used up, and can at the same time remove the products of waste. In higher organisms, the little masses of living material of which they are composed, and which are for the most part fixed, are nourished by a fluid in which they are bathed, fresh portions of it being supplied by its constantly flowing over them, instead of their moving like the amœba through it.

It will simplify our conception of this subject if we fix in our mind's eye one little mass of protoplasm or cell, and consider what changes will be produced in it by different conditions. Any alteration in the amount of the nutrient fluid, or in its composition, will necessarily produce a change in the nutrition of the living matter to which it is supplied. If nutriment be withdrawn, the cell will begin to burn away. If oxygen be withheld, (1) or the products of waste be not removed, combustion will cease, and the cell will die. If nutriment or oxygen be supplied in insufficient quantity, or the products of waste only partially removed, the cell may adapt itself to the altered circumstances, and its nutritive and functional processes go on in the same way, but to a less extent than before; or they may become deranged—that is to say, the cell becomes diseased. The limits within which the cell can adapt itself to changes in nutrition are the limits of its health. The higher animals, however, are no mere aggregation of cells, each nourishing itself independently of the others; for each cell has its own peculiar function, each its special kind and amount of nourishment; and none must do either too much or too little work, none must have too much or too little nourishment, or the nutrition and functional activity of the body as a whole cannot be properly maintained. This delicate adjustment of the several parts to one another is secured by means of the nervous system, which regulates at once the activity of any organ, the quantity of nutritive fluid supplied to it, and the amount of material it shall take up. The means by which it acts are, its direct influence on the nutrition of cells themselves,(2) as is seen in the salivary glands ;(3) or its indirect action through the circulation in slowing or quickening the heart, which propels the blood, in contracting or dilating the vessels which convey it to any part, or the capillaries which allow the actual nutritive fluid or lymph to filter out(4) and bathe the tissues. Besides thus regulating the supply, it also regulates the composition of the nutritive fluid by maintaining a due relation between the activity of the body, the supply of new material by digestion, and the separation of effete products by the excreting glands. On account of this mutual dependence of all the parts of the body on one another, if one gets wrong, it puts the others out of order. Thus a sudden chill may act on the vaso-motor nerves, and cause contraction of the vessels of the skin; and the blood they contain is thus thrown back on the internal vessels,(5) and congestion and inflammation of the kidneys ensue. In consequence of this, they no longer excrete as they ought the effete products, which then accumulate in the blood, react on the nervous system, and this again on the muscles; and so the circle goes on. In the case supposed, the renal arteries have not had power to contract sufficiently to resist the increased pressure and prevent congestion; while in another they might have done so, only allowing so much blood to pass as to increase secretion, and, by thus lessening the fluid in the blood-vessels, to counteract the effect of vascular contraction in the skin, restore the normal pressure, and preserve health. When all the organs are able to accommodate their nutrition and function to great alterations, we say the health is strong; but when they can only do so to slight ones, we say the health is weak; and when this is the case with one organ alone, we say that it specially is weak.

EFFECT OF DRUGS.—The nutrition of a cell may not only be altered by changes in its supplies of nutriment and oxygen; but it may be modified or destroyed by the addition of certain substances to the nutrient fluid. Thus a weak solution of alkali may increase or diminish the rapidity of the changes which it undergoes, by hastening the removal of waste products if they be acid, or retarding it if they be alkaline; while a weak acid will have an opposite effect. Certain metallic salts may stop them altogether by forming a firm compound with the substance of the cell, while other bodies may enter into combination with it for a time (possibly replacing some ordinary ingredient of its nutriment), again passing out and leaving it in its primitive condition, but altering during their stay its physical characters and functional properties. Such seems to be the case with curare, which, when injected into the blood, paralyses the peripheral ends of motor nerves; but, if life be preserved by artificial respiration, the poison is excreted, and its effect passes off. No change can be noticed in the nerve-fibres, either by the naked eye or microscopically, during the paralysis; and this was supposed to show that great functional alterations may occur without any structural change. But this is not the case; for Kühne (Stricker's *Histology*, Power's translation, vol. i, p. 221) has ascertained that, when the ends of motor nerves in muscles are examined microscopically, their outline is found to be more distinct during the action of the poison. It is possible that the change in physical properties shown by this distinctness of outline may be only the indication of some more important alteration in their chemical composition; but, whether it be more chemical or physical, a change at any rate takes place; and to this, I believe, we must attribute the alteration in function.

Whatever be the composition of protoplasm, the substances which are associated with it in the composition of different cells are at any rate different; and, although the same nutritive fluid is supplied to them, they do not all take out from it, or give out to it the same substances in the same proportions, but some take up more of one thing, and some more of another. And they do just the same with drugs added to the nutritive fluid. Thus lime-salts naturally exist in the blood, and are carried by it to every part of the body; but, while the bone-cells take them up in large amount, nerve-cells assimilate an almost infinitesimal quantity. And if we feed an animal on madder, which has an affinity for lime-salts, the bones become deeply stained, while the nerves and fat retain their normal colour. (6) It is possible, too, though experiments on this point are wanting, that a substance added to the nutritive fluid may be taken up by two structures, but may have a very different effect on the one from what it has on the other; just as a grain of sand, which would have no effect on the machinery of a locomotive, may totally stop the movements of a watch. We do not know whether sulphocyanide of potassium and curare are taken up equally by nerves and muscles or not; but the former salt will paralyse the muscles without affecting the nerves, while curare will paralyse the nerves, but leaves the muscles intact. (7)

The cells composing one structure, then, take up and are acted on by some drugs, and not at all by others; while other structures are much affected by the very substances which had so little action on the first.

DIRECT AND INDIRECT ACTION.—When any drug is taken up by a structure and acts upon it as curare on the ends of motor nerves, we term this its *direct* action. But, as all parts of the body are dependent on one another, some other structure may be affected, not by the action of the drug upon it, but by that which it has exerted on the first part. This is its indirect action. Thus, when curare has been given to an animal, it occasionally happens that the nerves going to the respiratory muscles become paralysed before those which go to the extremities.(8) The muscles of respiration then cease to act, the blood is no longer arterialised, carbonic acid accumulates, and, by irritating the nerve-centres, produce convulsions, which cease when the action of the poison extends to other nerves. In this case neither the muscles, the blood, nor the nerve-centres, are acted on directly by the curare. The muscles will contract if stimulated, and, if the lungs be artificially supplied with air, the blood will be arterialised as usual, the convulsions will cease, and life may be preserved. The non-arterialisation of the blood, the occurrence of asphyxial convulsions, and death, are thus due to the *indirect* action of curare.

LOCAL AND REMOTE ACTION.—Before curare could reach the nerves on which it acted directly, it was necessary for it to enter the circulation, but it had no marked action on the spot whence it was absorbed. Other substances, however, produce an effect on the spot to which they are applied, and this may be independent of any effect which they produce after absorption. This is termed their *local* action. Thus strong sulphuric acid taken into the stomach combines with its tissues and forms a slough: this is its local action. But besides this, the irritation in the stomach produces through the nervous system a weakening effect on the heart, the circulation stops, and the person dies. It is not the sulphuric acid which has found its way into the circulation and acted on the heart, but the irritation in the stomach conveyed to it through its nerves. This is the *remote* effect of the acid.

DOSE.—The effect produced by any remedy depends on several conditions. The first of these is the *amount existing in the blood* at any given time, which we may call the *actual dose*, to distinguish it from the usual dose administered by the stomach or otherwise, a part of which may not be absorbed, but remain inert at the point of introduction. The action which a drug has on the body is not dependent on its absolute amount, but on the proportion it bears to the body on which it is to act, so that an amount which is a small dose for one person is a very large one for another. (6) Thus if a grain of some active substance be injected at the same time into the veins of a full-grown man and into those of a boy of only half his weight, it will be distributed through twice as much blood in the man as in the boy, and each tissue will only receive half so much of it. The dose of a drug must therefore be regulated by the weight of the patient; and thus women, being lighter, require a smaller amount than men, and children less than adults. Though it would be more exact, it is not always convenient, to weigh patients; but in experiments on animals the weight of the animal should always be carefully ascertained, as well as the amount of the drug administered. If a substance be injected into the veins, the whole of it mixes with the blood and becomes active immediately, and the maximum effect is thus at once obtained, and will again diminish as the substance is excreted. But the case is different if it be injected subcutaneously, and still more if it be given by the stomach or any other mucous cavity; for as soon as some of it is absorbed excretion begins, and thus part of the drug is passing out of the blood while another part is being taken in. The amount in the blood is, then, *only the difference between that absorbed and that excreted in a given time*, and absorption may be so slow or excretion so quick that there is never a sufficient amount of the substance in the blood to produce any effect. Thus Bernard found(7) that a dose of curare which would certainly paralyse an animal when injected into the veins or even subcutaneously, would have no effect when introduced into the stomach; and Hermann(8) showed that this was due to the kidneys excreting the poison as fast as it was absorbed from the stomach, by tying the ureters, when the animal became paralysed as surely as if the poison had been introduced at once into the veins, though not so quickly. The more rapid the absorption, or the slower the excretion, of any drug, the greater will be its effect. Thus the effect produced by the same dose of a medicine will be in proportion to the rapidity of its absorption from the different parts to which it has been applied, unless the differences be so slight or the excretion so slow that there has not been sufficient time for the removal of any considerable quantity from the blood. On this account we must diminish the dose of a medicine in order to obtain the same effect, according to the rapidity of absorption from the place to which we apply it. Absorption is quickest from a serous membrane, then from intercellular tissue, and lastly from mucous membrane. The vascularity and rate of absorption from intercellular tissue is greater on the temples, breast, and inner side of the arms and legs, than their outer surfaces or back.(9) It should not be forgotten that any drug introduced into the stomach but not absorbed into the blood is as much outside the body as if it were in the hand, for any effect it will have on the system, provided always it have no local effect on the gastric walls. By the differences between absorption and excretion under different circumstances or in different individuals, the cumulative action of drugs, the effect of idiosyncrasy, habit, climate, condition of body, as fasting, etc., disease, and form of administration, can to a great extent, though not entirely, be explained; but experiments on some of these points are deficient, and the explanations now given are to some extent theoretical.

CUMULATIVE ACTION.—If a substance be naturally so slowly excreted from the body that the whole of the dose in ordinary use is not excreted before another is given, the amount present in the body will gradually increase, just like the curare in Hermann's experiment, and will produce an increasing or cumulative effect. Examples of this are to be found in metallic preparations, such as those of mercury or lead, which are excreted very slowly, or in some of the organic alkaloids, such as digitaline, if given in sufficiently large and frequent doses. The size of the dose and the frequency with which it must be repeated in order to produce a cumulative effect will differ acccording to the rapidity with which the drug is excreted; for, if excretion be rapid, a larger dose, or more frequent repetition, will be required. The long time which elapses before a dose of opium takes effect on some individuals is probably due to its being very slowly absorbed; and the power of one man to take, without apparent effect, an amount of alcohol or opium which would intoxicate another, to its either being more slowly absorbed from the stomach or intestine, or more quickly excreted by the lungs, skin, or kidneys, so that the amount present in the blood at any one time is never sufficient to produce toxic effects. If excretion from the skin and lungs be stopped, as by going from a warm room into the cold air outside, while alcohol is still being absorbed from the stomach, the amount of it in the blood is increased just as with curare,(8) and intoxication ensues.

EFFECT OF HABIT, CLIMATE, FASTING, AND FORM OF ADMINISTRATION.—The effect of habit in lessening the action of drugs may be due to increased power of excretion or diminished absorption; and that of a warm climate in increasing the action of narcotics, such as hyoscyamus, to their excretion being hindered by the diminution in the amount of urine consequent on the increased cutaneous transpiration. A medicine taken by a fasting person is generally more rapidly absorbed and has a greater effect than if the stomach be full, as is well known in the case of alcohol. The form of administration has also an effect on the rapidity of absorption. When a drug is given in a soluble form in small bulk it is more quickly absorbed, and will have greater effect than when given in an insoluble form or much diluted. So a glass of brandy will have a greater and more rapid effect if taken raw than if diluted with a large amount of water; for if three times its bulk of water have been added to it, the stomach must absorb four times as much fluid before the same amount of alcohol could enter the blood-circulation : at the same time the greater amount of water in the blood increases excretion by the kidneys, and thus we have the actual dose of alcohol diminished both by slower absorption and by quickened excretion. It must not, however, be forgotten that the action of alcohol in the blood is complicated by its local effect on the stomach, and this is greater when it is given undiluted.

LARGE AND SMALL DOSES.—The effect produced by a small dose of a drug is sometimes exactly the opposite of that produced by a large one. We cannot say exactly why it is so; but we very generally find that any substance or any condition, whether it be acid or alkali, heat or electricity, of which a moderate amount increases the activity of cells, destroys it when excessive.(1)

HOMŒOPATHY.—This opposite action of large and small doses seems to be the basis of truth on which the doctrine of homœopathy has been founded. The irrational practice of giving infinitesimal doses has of course nothing to do with the principle of homœopathy—*similia similibus curantur:* the only requisite is that mentioned by Hippocrates, when he recommended mandrake in mania ;(10) viz., that the dose be smaller than would be sufficient to produce in a healthy man symptoms similar to those of the disease. Now in the case of some drugs this may be exactly equivalent to giving a drug which produces symptoms opposite to those of the disease ; and then we can readily see the possibility of the morbid changes being counteracted by the action of the drug and benefit resulting from the treatment. For example, large doses of digitalis render the pulse extremely rapid, but moderate ones slow it. In this instance its moderate administration when there is a rapid pulse is homœopathic treatment, and this has sometimes been beneficial. But it is not proved that all drugs have an opposite action in large or small doses, and homœopathy, therefore, cannot be accepted as an universal rule of practice.

CONSTITUTION AND IDIOSYNCRASY.—Variations in the action of a drug cannot be entirely explained, however, by the varying amount in which it may be actually present in the circulation and acting on the body. Another modifying element of great power is *constitution.* In animals generally, we have certain arrangements for producing motion, others for the regulation of these, and others, again, for supplying them with the material necessary for the performance of their functions. But the parts which enter into each of these are not equally developed in all animals; in some one part preponderates; in others, another. Even in animals of different species, and in individuals of the same species where the relative size of organs seems the same, differences nevertheless exist; and the presence of a few cells more or less in a ganglion, and a few fibres more or less in a nerve, may alter to a very great extent the action of any substance on the organism. When a medicine given to one person produces an effect slightly differing from that which it generally causes, the difference is said to be due to *constitution;* when its difference is great, it is said to be due to *idiosyncrasy*. Now, these effects may be merely due to differences in absorption and excretion, as has been already explained, or to the different *relative development* of other parts, especially parts of the nervous system. It is easy to understand the altered effect which may be thus produced, and to perceive the ambiguity of such terms as "nervous stimulant", when we recollect that different parts of the nervous system act exactly in the opposite way to others; and if anything should act on both of these, it will produce an opposite effect according as one or other part is more developed and more powerful. Thus the vagus nerve has the power of rendering the heart's action slow, and the sympathetic of quickening it; and any drug which irritates them both, will make the heart's action slow if the vagus be more developed, or quicken it if the sympathetic be stronger. Thus two horses of unequal strength, pulling in opposite directions, may counterbalance each other; but if both be struck with a whip at the same moment, the power of the stronger becomes evident, and he pulls the weaker after him.

A good example of this action is given by muscarin, an alkaloid obtained from a poisonous mushroom, *Agaricus muscarius.* Professor Schmiedeberg, of Dorpat,(11) has shown that this alkaloid produces great irritation of the vagus nerve, so that in frogs the heart will stand still for hours together. When given to dogs, it sometimes makes the pulse slow, but sometimes it quickens it; and one might therefore be inclined to say that when it produces quickening it cannot be acting on the vagus. But the explanation of this phenomenon is, that muscarin does not act on the vagus alone, but has also an effect on the vaso-motor nerves, producing dilatation of the vessels and diminution of the blood-pressure in them. Now, lessened pressure acts as a stimulant to the sympathetic, and quickens the heart. In this way, muscarin stimulates both vagus and sympathetic, and the pulse is rendered quick or slow according as the power of the one or other is greater in the particular dog to which it is given. In frogs, the blood-pressure has no great action on the heart, and in them the effect of the vagus is not interfered with.

Another instance may be given where an apparent difference in the effect of a drug on two animals may be removed by reducing their organs to the same condition. In most animals, the slowing action of the vagus on the heart is constantly exerted during health; and when it is cut the heart beats much faster. But in the rabbit, its power is comparatively small, and the increased rapidity of the pulse after its division is but slight. In most dogs, on the contrary, its power is great, and, if it be cut, the heart beats very much quicker, and sends more blood into the arteries, so as to raise the pressure in them. If we measure the pressure of the blood in the arteries of a rabbit and of a dog, and then cause them to inhale nitrite of amyl, we find that the small vessels have become widened and allow the blood to pass easily out of the arterial system into the veins, so that the pressure sinks considerably in the rabbit, but it sinks only slightly in the dog. The effect seems at first sight different; but when we examine it more closely, we find that the heart of the dog is no longer beating slowly, but very quickly, so as to keep up the pressure, notwithstanding the rapid flow of blood through the widened vessels, while the heart of the rabbit was going so fast before that it could not go much more quickly. If we cut the vagi in the dog, so that the heart goes as quickly as in the rabbit before it begins to inhale, the blood-pressure sinks during the inhalation, just as it does in the rabbit.(12)

I have given these examples at length, because of their important bearing on the question how far conclusions as to the action of medicines on man may be drawn from those which they exert on the lower animals. Now, the action of curare in paralysing the ends of motor nerves is one of the simplest and least complicated examples that we can take, as the very nature of its action prevents disturbances in other systems from showing themselves; and we find that it is exactly the same in the Indian who accidentally wounds himself with his poisoned arrow, in the game which he shoots, or in the frog on which we experiment.

Motor nerves, the structure on which curare acts, are alike present in all, and in all are its results the same.

And as we have seen that, in the lower animals, differences in the action of drugs are produced by differences in the structure of the animal, and that the former disappear when the latter are removed, we are, I think, justified in concluding that, when the organs or structures on which a drug acts are similar in man and the lower animals, the action will be alike, and that variations will be observed just in proportion to the difference between his structure and theirs. But as it may be difficult or impossible to detect these differences except from their effects, we ought to test our conclusions as to the action of remedies by giving them to a healthy man, and observing whether their effects are such as we have been led, from our experiments on animals, to expect.

DISEASE.—The different effects of a medicine in disease from those produced by it in health may be partly due to differences in the dose actually present in the blood from altered absorption and excretion, and partly to the alterations produced by disease in other organs, which may interfere with their direct, and probably to a much greater extent with their indirect, action. But what the alterations in each disease, and the ways in which they will modify either the direct or indirect action of remedies, really are, can only be determined by an increased knowledge of pathology and by actual clinical observation.

CHEMICAL CONSTITUTION AND PHYSIOLOGICAL ACTION.—I have spoken thus far only of the changes in the body and the various effects which they produce; but I must not leave this subject without mentioning the wide field of research which has been opened up by the remarkable discovery made by Drs. Crum Brown and Fraser,(13) of the relation which exists between chemical constitution and physiological action. It was known before that one drug would act only on one part of the body, another on another part; but they have shown that changes in the chemical composition of a drug may not only alter its action, but transfer it to a different structure: so the addition of sulphate of methyl to strychnia, brucia, or thebaia, causes them to act on the terminal branches of motor nerves instead of on the spinal cord, while a similar addition to other alkaloids removes some of their actions but leaves others unchanged. Further researches of this kind may enable us to determine what parts will be acted on by a drug after a definite change has been effected in its chemical constitution; and the progress of physiological chemistry in ascertaining the composition and properties of the tissues renders it not impossible that such knowledge may yet be acquired as that spoken of by Locke in the following words. "Did we know the (mechanical) affections of the particles of rhubarb, hemlock, opium, and a man, as a watchmaker does those of a watch, whereby it performs its operations, and of a file, which by rubbing on them will alter the figure of any of the wheels, we should be able to tell beforehand that rhubarb will purge, hemlock kill, and opium make a man sleep." And even though our knowledge should never reach this extent, the rapid advances which it has made of late years, the power of altering the chemical composition of the organic alkaloids, and along with it their physiological action, which we now possess, and the fact that one of them (conia) has already been made synthetically, (14) incline us to believe that we may by and bye make substances which will produce the physiological effects which we desire, and that a future lies before therapeutics of which at present we can hardly dream.

II.—ACTION OF DRUGS ON PROTOPLASM: GENERAL DIRECTIONS FOR EXPERIMENTAL INVESTIGATION.

Modes of Experimenting.—Caution.—Action of Drugs on Protoplasm.—Action on Vibriones and Bacteria.—Contagium Vivum.—Action on Fungi; on Fermentation; on Putrefaction; on Oxidation; on White Blood Corpuscles; on Inflammation.—Action of Gases.—Steps of an Investigation.—Administration of Drugs.—Observation of Effects.—Interpretation of Results.—Minimum Fatal Dose.—Various Channels of Administration.—Excretion.—Mode of securing Animals.—Instruments required.—Mode of making Cannulæ, T-tubes, and Pens.—Narcotising Animals.—Action of Narcotics.—Introduction of Cannulæ into Vessels.—Injection of Fluids.—Division and Irritation of Nerves.—Artificial Respiration; in Mammals; in Frogs.—Administration of Gases or Vapours.

GENTLEMEN,—In experimenting on the effect of drugs, our great object must be to *localise* their action—to be able to say with certainty, This is the organ on which this medicine acts, and such and such is the action which it exerts upon it. There are two ways in which this might be done.

1. We might give the medicine to animals of all kinds, from those consisting of one simple cell upwards to the highest forms of life, and mark how its action became modified as we advanced farther and farther from the simple mass of sarcode, and organ after organ became differentiated and developed. Unfortunately, however, the knowledge of comparative anatomy and physiology which is required to interpret the effects that we might thus obtain is so great, and possessed by so few, that this method is at present of little use.

2. We might take a highly organised animal, not very unlike man in its general structure, and, by operative procedures, allow the medicine to act now on one and now on another part of the body, but never on all at once, till we find out those parts for which it has a particular affinity.

This second method is the one which we chiefly employ, but sometimes we may very conveniently use them both, as in the case of protoplasm, the physical basis of life.

CAUTION.—As I intend not only to describe the ways in which experiments on the action of medicines are to be performed, but also to give examples of the conclusions drawn by various observers from the experiments which they have made, and of the way in which these conclusions have been applied, I take this opportunity of strongly warning you, once for all, that you must distinguish very carefully between the observations actually made by any one and the conclusions which he draws from them. Observations on the effect of a drug may be correct, and yet the theory of its mode of action be erroneous; and both of these may be right, and still the proposed application of it to a disease may be valueless from ignorance of its real pathology. All observations, too, are not to be taken as facts : they must be confirmed by frequent repetition either by the first observer himself or by others before they can lay claim to this title. Their value depends to a great extent on the observer, and is in proportion to his power of seeing correctly what is before him, and the exactness of his description of what he he has seen. Perhaps erroneous statements are due in great measure to the results of experiments not being noted at the time when they were done, but written down from memory some time afterwards. When this is the case, they lose in a great measure their claim to the name of observations, and they become merely thoughts or ideas of the observer. *All experiments should be noted down at the time when they are performed;* and if they are not, the time which elapsed before they were written should be stated, that future workers may know what value to attach to the observation, and not be put to the unnecessary trouble of disproving it if it be erroneous. Before beginning an investigation, it is convenient to write out the questions which we propose to ourselves, and to note down what experiments will be necessary to answer them. We are thus less likely to make experiments at random, and to waste time without coming to any certain conclusion.

ACTION ON PROTOPLASM.—We may study the action of drugs on protoplasm either in unicellular organisms like the Infusoria, in cilia, in white blood-corpuscles, or in those minute bodies—bacteria and vibriones—to which attention has of late been so much directed, and which, despite their minuteness, possess so much importance from their power of producing fermentation and decomposition in dead organic matter, and not improbably of causing disease in living beings. For the purpose of studying it in Infusoria, we prepare an infusion of hay some days before we wish to experiment, and a solution in water of the drug which we wish to investigate. We then heat a piece of glass tubing in the middle, draw it out and cut it across, so as to obtain two little pipettes, which will deliver drops of nearly equal size. From one of these we let fall a drop of infusion of hay on a glass slide, and examine it under a low power of the microscope without a covering glass. We then let fall a drop of the solution of our drug upon it, mix the two drops well with a glass rod, and again examine them microscopically to see whether or not the infusorial animalcules are still moving. If they be moving, and continue to do so for some time, we prepare a stronger solution of the drug; but if they have completely stopped when we looked, we make a weaker one, and again mix a drop with one of hay-infusion, repeating the experiment till we have got a solution of such a strength that a slight movement of the animalcules can be observed just after mixing the drops, but ceases almost immediately, and cannot be brought back by adding water. We can then compare the action of different drugs by observing of what strength the solution of each must be, in order to produce precisely this effect.(15)

Professor Binz of Bonn has found in this way that certain substances, such as common salt, chlorate, chloride and bromide of potassium, alum, etc., appear to stop the movements of infusoria by altering the amount of water which they contain, as strong solutions cause them to shrivel at first, and then to swell up and become motionless. Weaker ones make them swell likewise; but their effect at first is different, as they do not shrivel up the animals, but, on the contrary, render their movements more lively.

Other substances kill them in a way which we do not understand, stopping the movements at once without producing any apparent change in the animal's body to account for it. The most active of these substances are chlorine, bromine, corrosive sublimate, iodine, permanganate of potash, and creasote. After these comes quinine, less powerful than they, but far more so than other organic alkaloids. Even strychnia, so fatal to higher animals, has barely one-fourth the power over these lower organisms which is possessed by quinine, a substance which is dangerous to mammals only in such large doses that we are accustomed to look upon it as a remedy, but hardly at all as a poison.

ACTION ON VIBRIONES AND BACTERIA.—If a piece of boiled meat or white of egg be allowed to lie in water for a few days, or a little of Pasteur's solution be exposed in a glass, the fluid becomes milky, and vibriones and bacteria are formed in large numbers. Pasteur's solution is made by dissolving ten *grammes* of sugar, five *decigrammes* of tartrate of ammonia, and one *decigramme* of yeast-ash, in one hundred cubic *centimetres* of water; or a little white of egg may be added to the hay-infusion, when the infusoria soon disappear, and it remains full of bacteria and vibriones.(15) A drop may now be taken, diluted with another drop of water, and the action of drugs on vibriones examined in the same way as on infusoria.

In this way it is found that the same substances which kill infusoria also prove destructive to vibriones and bacteria: and if they kill these organisms when outside the animal body, they should do likewise when they are inside, and thus cure diseases which may be caused by their presence. Now, bacteria have been said to be the cause of malignant pustule, and they are at all events frequently present in large numbers in the blood of animals affected by it, and their destruction can hardly fail to be advantageous. We are, therefore, not at all surprised to learn that Bouley and the French Commission found (*Compt. Rend.* lxviii, 82) that, while all animals which they inoculated with this disease died when left to themselves, four recovered out of five to which they had given carbolic acid, and that other cases treated in the same way by others gave a like favourable result. The striking correspondence between the effect actually produced on the disease and that which we would expect from its action on bacteria, which we suppose to be the cause of it, seems also to be an evidence of the truth of the hypothesis that bacteria are the cause of the disease, and that carbolic acid cures it by killing them. Before we accept this as a fact, however, we should test it by adding to one portion of the blood of a diseased animal, carbolic acid in the same proportion as it was likely to be present in the blood of the one cured, and comparing it with another portion to which none had been added, and see whether the amount was sufficient to have any action on the bacteria. If it were not sufficient, we should have to look for some other action of the acid to explain its effect.

As cases of malignant pustule or other diseases in which bacteria and vibriones are found in the blood happily do not present themselves every day, Binz(16) produced fever in dogs artificially by injecting infusion of hay or putrid animal matter into their veins, and then tested the action of quinine by injecting it either at the same time or shortly afterwards. The quinine diminished the effect of the infusion, but not to the extent which he expected; and this he thinks due to the infusion not containing vibriones alone, but gases and other products of decomposition, whose action would not be affected by quinine. Whether this be so or not, must be decided by further experiments. He believes also that hay-fever is due to vibriones; and he cured Helmholtz, who had suffered from it for several years, by injecting a solution of quinine into his nostrils.

ACTION ON FUNGI.—When spores of the ordinary penicillium or mould-fungus are thrown into Pasteur's fluid or syrup, they grow and develope new spores. Two portions must be taken, and the drug to be tested added to one and none to the other, and the amount of it necessary to prevent the formation of spores must be noted. If carbolic acid, corrosive sublimate, or very strong solutions of quinine, be added to them, their growth is prevented.

ACTION ON FERMENTATION.—As butyric fermentation depends on the presence of vibriones(17) and alcoholic on the yeast-fungus, we should expect that substances which kill these would prevent fermentation. To test this, two glass-tubes or flasks are filled with a mixture of milk-water, grape-sugar, and chalk (from which carbonic acid will be set free by the lactic acid formed), or with a solution of grape-sugar or yeast. To one of them a certain amount of the substance to be tested is added, and both are then inverted over mercury and kept in a warm place for several days. The amount of gas developed is then measured; and, if the addition of the substance have hindered the production of gas, we know that it has hindered fermentation in the same proportion. It has thus been found that quinine, amounting to $\frac{1}{180}$th part of the mixture, completely stopped the development of vibriones or the production of gas; and other substances have a similar effect.

As many cases of indigestion, acidity, flatulence, vomiting, and summer diarrhœa, more especially in children fed by hand, are most probably due to the fermentation of starchy and saccharine food caused by vibriones,(18) Binz thinks that creasote, quinine, etc., are serviceable in their treatment by stopping this. As it is the local action that is wanted, the longer the medicine remains in the intestine before being absorbed, so much the better will its effect be; and thus the greater benefit derived from bark than quinine in some such cases might be explained.

ACTION ON PUTREFACTION.—The antiputrescent action of drugs is tested by putting a square of boiled white of egg into each of two vessels containing water and setting them in the sun. To the liquid in one vessel the drug is added, and the rapidity with which the edges of the square of white of egg on it become decomposed and soft is noted and compared with that in the other vessel. Instead of white of egg, a piece of meat or bread may be used. The relative power of different drugs in stopping putrefaction does not always correspond to the ideas which we would be inclined to form; for who would think that quinine would be more powerful than such antiseptics as creasote, chloride of lime, or arsenic? and yet such is said to be the case. So powerful is quinine, that a piece of meat placed in a solution of $\frac{4}{5}$ per cent. of the sulphate, with a little dilute acid, remained in summer without decomposition till the fluid was dried up. (19)

ACTION ON OXIDATION.—If fresh leaves of lettuce or dandelion are triturated with five or ten times their weight of water, with free access of air, the fluid filtered, and fresh guaiac tincture added to it, a blue colour is produced, showing that ozone is present in it. (20) To test the action of a drug on the formation of ozone, two portions of the filtered fluid are put in test-glasses, and the drug added to one. Both are allowed to stand for one or two hours, with occasional shaking, fresh guaiac tincture is dropped cautiously into both, and by the greater or less depth of blue produced in each fluid we judge of the amount of ozone present in each. In this way it is found that quinine diminishes or stops the formation of ozone in these fluids, and at the same time the little protoplasma-granules with which they abound are rendered motionless and altered in appearance. There seems to be some connection between these protoplasma-granules and the formation of ozone, as the stoppage of the one runs parallel with the alteration in the other.

Quinine seems to have the power of diminishing oxidation within the body as well as out of it, since when injected into the blood it lessens the excretion of urea and diminishes the temperature both in health and disease during life, and hinders its rise after death ;(21) and this action is apparently not due to nervous centres regulating temperature, or to changes in the circulation allowing quicker cooling by the skin.

ACTION ON WHITE BLOOD-CORPUSCLES.—To examine this, we take a drop of blood from the finger, put it on the under surface of a thin glass, and lay it over the opening in Stricker's warm stage (Stricker's *Histology;* New Sydenham Society's *Translation*, p. 13), and examine it with a high power of the microscope, such as Ross's $\frac{1}{12}$ or Hartnack's No. 10, at a temperature of 98° F. After satisfying ourselves that the white corpuscles are in active motion, we take a solution of the drug in fresh serum, or in half per cent. solution of common salt; mix a drop of it with the blood and examine again. Or we may use Max Schultze's warm stage, which consists of a flat piece of brass covering the stage of the microscope, and having a long arm projecting at each side and a thermometer in front. When a lamp is placed under one or both arms, they conduct the heat to the middle part on which the object lies, and thus warm it to any desired temperature. The drop of blood must be placed on a piece of glass three and a half inches long and two and a half broad, which is then laid on the warm stage.(22) The drop is next covered by a thin glass, and over all is put the lower part of a lamp-cylinder, through whose upper end the tube of the microscope slides, and round whose interior is put a piece of moist blotting-paper to prevent evaporation from the blood. The drug is applied as with Stricker's stage. Solutions of corrosive sublimate and veratria, even in very minute quantity, stop the movements of the white blood-corpuscles, but neither is so active as quinine. Strychnia is rather less powerful than any of these, and many other alkaloids much less so.

ACTION ON INFLAMMATION.—During inflammation, the white blood-corpuscles are very active, and crawl through the walls of the capillaries in much greater numbers than usual. It is, therefore, interesting to inquire what will be the effect on this of any drug that stops their motions. For this purpose we curarise a frog and lay it on a large plate of cork with a hole at one side, (23) and another piece of cork half an inch high at the other. We fix the body of the frog to the raised piece, open its abdomen with a pair of scissors, draw out the intestines, and fasten the mesentery with very fine pins over the hole. In an hour and a half or two hours afterwards, white corpuscles come rapidly out of the vessels and wander over the field. We may then inject our drug into the circulation or apply it locally to the mesentery.

Binz states that, when he injected quinine into the circulation, the number of corpuscles in the vessels became diminished, and they ceased to wander out, while those already out continued to wander further, so that, instead of being evenly distributed over the field, they left a clear space round the outside of the vessel, in which few were to be seen. If, on the other hand, it be applied locally, the corpuscles which are already out stop moving, while those in the vessel continue to migrate, and thus, instead of a clear space, a dense accumulation of corpuscles forms round the vessel. In order to produce this effect, $\frac{1}{25000}$ to $\frac{1}{20000}$th of the animal's weight of quinine is necessary ; and, if it were given to a man weighing 150 lbs., in order to stop the exit of corpuscles from the vessels in such a disease as peritonitis, three or four drachms of the medicine would require to be given within a short time. Binz's observations as to the effect of quinine on the white corpuscles have been confirmed by Martin, (24) but have been denied by Schwalbe, (25) so that farther investigations on this point are very desirable.

ACTION OF GASES.—This is examined by putting the cells to be examined on Stricker's warm stage, and bringing the gas into contact with

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them in the manner described by him (Stricker's *Histology*, Sydenham Society's edition, p. 8).

STEPS OF AN INVESTIGATION.—The animals which we chiefly use in experiments are frogs, rabbits, guinea-pigs, and dogs. In investigating the action of a drug, we examine—

1. What the symptoms are which a large dose produces.

2. Taking the most prominent symptom, we inquire (*a*) On what organ does the production of this symptom depend? (*b*.) How has it been affected by the drug? (*c*.) Has this affection been primary or secondary?

3. We examine other organs which we think may have been also affected.

ADMINISTRATION OF DRUGS.—To examine the general effect of a drug, we weigh the animal and then give it a large dose in our first experiment, in order to get exaggerated symptoms. It may be given by the mouth or by subcutaneous injection. In frogs, the substance may be injected either under the skin of the back or into the abdominal cavity. In rabbits, etc., it is most conveniently injected under the skin of the flank. In guinea-pigs, the abdominal parietes are very thin; and, if we wish to compare experiments with different doses, care must be taken not to push the point of the syringe into the abdominal cavity, as the absorption will be then more rapid, and the same dose produce a greater effect. If we wish to give the medicine by the mouth, we either put it well back on the root of the tongue and then hold the animal's jaws together till we think it has swallowed it, or we put a perforated cork between its teeth, push an elastic catheter through the hole in the cork down the œsophagus into the stomach, and inject the drug in solution through the catheter. Orfila used to introduce the drug into an opening in the œsophagus, which he then ligatured to prevent vomiting;(26) but since subcutaneous injection was introduced this method is rarely employed.

OBSERVATION OF EFFECTS.—After the drug has been administered, we allow the animal to move freely about, but prevent frogs from escaping by covering them with a large bell-jar. We then see whether the animal is restless or disinclined to move; whether its movements are perfectly performed or unsteady; whether or not its legs seem weak and paralysed, or convulsive movements or involuntary twitchings be present; whether its heart-beats or pulse, and respirations, are quick or slow, strong or weak; whether there is vomiting or purging diuresis; salivation; or dryness of the mouth; flow of tears, or dry conjunctiva; and whether the pupil be contracted or dilated. If the animal seem asleep, we pinch it to ascertain if reflex action continue after voluntary motion is gone ; and if respiration cease, we ascertain if the heart still continue to beat. As soon as possible after death, we open the animal and see if the heart still be beating. If it have stopped, we note whether its cavities are full or empty, its walls flaccid or firm, and try whether it will still contract or not on pinching or scratching it, or on irritating it by an electric current. We observe whether the veins are turgid or empty, the lungs pale or congested, the stomach and intestines quiet or in active peristaltic movement, the spleen large or contracted, the bladder full or empty ; and the urine may be tested for sugar.

INTERPRETATION OF RESULTS.—If we find in the course of these experiments that voluntary motion is increased or lessened, we may naturally conclude that the activity of the cerebrum is increased or diminished, unless the increase of motion should depend on pain, or its diminution on impairment of the motor apparatus. Unsteady movements, paralysis or convulsions, impaired reflex action on pinching, or stoppage of respiration before the heart, point to the spinal cord, to the nerves, or to the muscles; while quick or slow, strong or weak pulse, or stoppage of the heart before the respiration, point to the vaso-motor system or cardiac nerves; increased or diminished secretion, to secreting nerves; and full or empty bladder, and diminished or increased peristalsis, to the motor nerves of the bladder or intestine. We then try the effect of a small dose, and note in what respects it differs from that of a large one. We thus ascertain in a general way what the organ is, which is chiefly acted on by any drug, and afterwards proceed to investigate the nature of the action by a farther series of experiments.

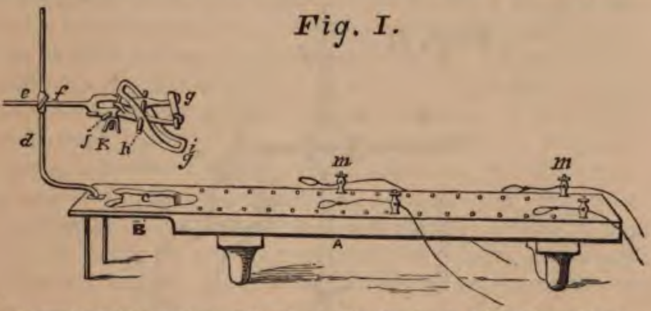
MINIMUM FATAL DOSE.—If the drug be poisonous, we then try to ascertain the minimum fatal dose. For this purpose we weigh an animal and inject into it a dose which we think will not prove fatal, wait a short while, and then inject more till death is produced. We then reckon how much of the drug has been injected for every pound weight of the animal. We take another animal, and inject into it *at once* a quantity which will be somewhat smaller for its body-weight than that given to the first. The reason why a somewhat smaller quantity should be taken is, that some time was allowed in the former experiment for the excretion of part of the poison between each dose. If this amount prove fatal, we must give a still smaller quantity to another animal ; but, if not, we must give more till we find the smallest quantity which will kill.

VARIOUS CHANNELS OF ADMINISTRATION.—The next point to be determined is, whether the effects are the same when given by the mouth or rectum, or other mucous surfaces, as by subcutaneous injection. If we should find, as Bernard did with curare, that a substance which is active when injected subcutaneously or into a vein, has no effect when introduced into the mouth, rectum, eye, or bladder, we must determine whether this is due to want of absorption or to decomposition of the drug by the secretions with which it becomes mixed. This is done by mixing it with these secretions, such as urine or gastric juice, allowing it to stand some time at the temperature of the body, and then injecting the mixture subcutaneously, and observing whether the usual effect is produced or not; or by ligaturing the ureters to prevent excretion.

EXCRETION.—Lastly, we examine in what manner it is excreted from the body. As most solids are excreted by the kidney, we generally restrict this process to evaporating the urine, or testing it either chemically or by injecting some of the extract into another animal.

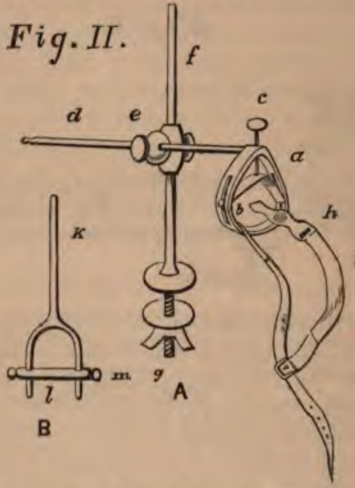
MODE OF SECURING ANIMALS.—In order to determine in an exact manner what organs or parts are affected, we are obliged to make use of apparatus of various kinds; and, before these can be applied to an animal, it must be prevented from moving. Frogs are fastened to a frog-board by a piece of cord with a noose at the end, slipped over each elbow and ankle. The frog-board may consist of a piece of mill-board about nine inches long by three inches broad, with four slits at the sides to keep the cords in position, or of a piece of wood the same size, and from a quarter to half an inch thick, with holes, through which the cords are passed. They may be fastened by simply tying them together or by sticking a small wooden pin into each hole, or by four screws, such as are used by fastening the wires of galvanic batteries, placed in the edges of the board. The last way is, I think, the most convenient. Rabbits are best secured by Czermak's holder and board (shown in fig. 1). The best cord is strong window-cord. The one end should be flattened with a hammer, and turned over so as to make a small loop, whose two sides are then firmly bound together with waxed thread. Through this loop the other end is passed, and the noose thus made is ready to be drawn tight at any moment. The other end of the cord should be cut to a point and also bound with waxed thread to prevent the strands unravelling. The rabbit is placed on the board, the nooses slipped over the legs and drawn tight, and the ends of each cord passed through the screw which will be nearest it when the animal lies on its back. The rabbit is then turned over, and the cords drawn through the screws and fastened. The bar *h* is then put between its teeth, and the screw *l* turned till *g* and *g'* fit tightly over its muzzle, and the projecting ends of *g* fixed into the ends of *f*. Dogs may be fastened by Bernard's holder (fig. 2A), or by a simple bar of iron put behind their canine teeth. A piece of cord is first tied round the upper jaw, the bar put into the mouth, and the two jaws tied firmly over it. A split strap may be used instead of the cord. I have had a bar made with a hole at each end, into which a fork of steel passes, and is secured by a screw. The fork may then be fastened by a nut to an upright rod, as in Czermak's holder (fig. 2B). Cats and guinea-pigs may be fastened by Czermak's holder. For guinea-pigs, a little padding must be placed between *g* and *g'* in order to make them catch the head. A simple bar and cord may also be used for rabbits, cats, and guinea-pigs, as well as for dogs.

Fig. I.



Czermak's Rabbit Holder and Board. A. The board. B. A bent piece of iron forming the upper part of the board. *c.* An open space through which instruments can be introduced from below to divide the spinal cord. It is generally covered by an iron plate. D is an upright rod fixed by a screw into a slit in B. *f* is a forked rod, which can be moved back or forward, up or down, by the nut *e*. The forks are hollow, so that the ends of the holder can be passed into them and fastened by the screw *j*. *h* is a bar which passes behind the incisor teeth of the rabbit. *g* and *g'* are two bent bars which pass under the chin and over the nose of the animal, and are brought together by the screw *l*. From the upper end of *g'* hangs a screw, which passes between two projections on *g*, and has a mother-screw *k*. The screw *k* works against the projections on *g*, and draws the ends of *g'* and *g* together. These press on the rabbit's nose and under jaw and keep the teeth firmly locked over the rod *h*. *m m* are screws for fixing the cords which confine the legs. They are a remarkably convenient sort, consisting of an outer part with a horizontal hole, and an inner ring with a stalk on which a milled screw plays. When the milled head is at the top of the stalk, the inner ring and outer holes correspond, and the cord can then be easily pushed through; but when the milled head is turned, the stalk and ring are drawn up and the cord nipped between it and the outer part. The cords may either be fastened directly in the screw or passed first through one of the holes in the edge of the board. The board should be covered with a large pad of India-rubber stuffed with horsehair, and there should be another round pillow to put under the animal's neck.

Instruments Required.—The instruments which we generally require for operations are—sponges, one pair of large scissors and one small pair, cutting well at the points, scalpels, forceps, small bull-dog forceps with smooth points, blunt hooks, a small aneurism-needle, flattened sidewise and with a rounded point (fig. 3 G), ligatures, finder (a kind of probe set in a handle to open up the lumen of a divided vessel), syringe, cannulæ, a piece of card, small whalebone-probe, and one or two swine's bristles. As these are very apt to be mislaid during an operation, I find it convenient to have a small wooden tray about three-quarters of an inch deep, with thin upright sides, and divided into compartments, one for each kind of instrument. It is advisable, also, to have an extra instrument or two of each sort.



A is Bernard's dog-holder. *a* is a metal ring, within which a bent piece of metal, *b*, is moved up and down by the screw *c*. *h* is a straight piece, which is fastened by a screw to *a*, and can be moved nearer to or farther from a corresponding piece at *b*. These two pieces lie under the lower jaw of the dog; the bent piece *b* is screwed down on its nose, and the strap *i* buckled behind its head, which is thus firmly fixed. It may be moved back or forward by sliding the rod *d* through the nut *e*, or up and down by moving *e* on *f*, which is a strong iron rod fastened to a table or board by the screw *g*.

B. Brunton's holder for dogs or rabbits. A loop of cord is tied round the upper jaw, the bar *l* passed behind the canine teeth of the dog or cat or incisors of the rabbit, and the two jaws then tied together to prevent its slipping out. This mode of fastening animals has been long used, and my modification simply consists in the addition of the forked bar *k*. After *l* is fastened in the mouth, the forked ends of *k* are pushed through holes in *l*, and fastened by the screws *m*. *k* may then be fastened to an upright bar by means of a nut in the same way as Bernard's or Czermak's holder.

WAY OF MAKING CANNULÆ.—Cannulæ for injecting into vessels may be made of metal (fig. 3 C) or of glass. Glass ones can be easily made of any size required by heating a piece of glass-tubing over the flame of a blow-pipe, and drawing it out in the middle, as represented by the dotted line (fig. 3 D.) It is then heated at *a* and slightly drawn out, so that a bulging piece is left between *a* and *c*; it may then be heated and very slightly drawn out at *b*, then cut with a three-cornered file at *c*, and the point ground obliquely off on a hone. If the point be at all sharp, its edges may be rounded in a gas-flame. When the cannula is introduced into a vessel, a ligature at *a* prevents it from coming out: it may be connected with a syringe or with any piece of apparatus by a piece of India-rubber slipped over the other end and tied at *b*. A cannula for connecting an artery with a kymographion may either be of this sort, or may be made of metal of the shape shown in fig. 3 A. As it is difficult to hold it with forceps, it should be put on a piece of wood or whalebone of the shape shown at B. This both holds it firmly, and the point entering the vessel allows the cannula to be more readily pushed on into the lumen. A few notches on the side of the cannula prevent the vessel and ligature with which it has been tied from slipping off the end. By means of the little ear at *e*, it can be tied to the tube, on to which it is fitted.

MODE OF MAKING CANNULÆ, T-TUBES, AND PENS.—Cannulæ for the trachea are made by closing one end of a tube, directing a small blow-pipe flame against a point in its side till it is quite soft, and then suddenly blowing into it. The soft part expands into a thin bulb, which is scraped off, and a hole remains in the side of the tube. The object of this hole is to allow the air to escape during expiration. Instead of a hole in the cannula, one may be cut in the side of the India-rubber tube to which it is connected; but this is more apt to be accidentally closed. The tube is then drawn out into the form seen at Fig. 4 A, cut off at both ends, and one end ground obliquely off on a sandstone with some water.

A knob may be made at the ends of other cannulæ for various purposes, by heating the end and striking it against a piece of glass or iron, or by heating the end in a flame, continuing to blow steadily through the tube while you do so.

T-tubes are made by blowing a hole in the side of one tube, in the same way as for a respiration-cannula; and then putting the heated end of another tube over it while the first is still hot, so that the two stick together. The joint must then be annealed by heating it in an ordinary gas-flame, reducing the size of the flame gradually, so that the glass may cool very slowly.

Pens for use with a kymographion are made by drawing tubes to a point, as shown in Fig. 3, E and F; and grinding the point on a fine hone, and rounding it, if necessary, in the flame.

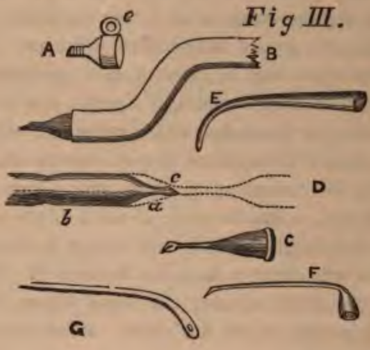


Fig III.

A is a metal cannula with an ear *e*, by which it can be fastened to any tube connected with its large end. B is an instrument for introducing A into a vessel. It consists of a piece of metal tubing, with a pointed piece of wood at one end, over which A is put. The point projects through the smaller opening in A, so as to enter the lumen of the vessel readily. C is a metal cannula which fits on the end of a syringe for injecting fluids into vessels. D is a glass cannula. The dotted line shows the original tube drawn out in the blowpipe-flame; the darker line shows the finished cannula. E and F are two pieces of glass tubing drawn out to make pens. They may be attached by pieces of cork to any writing apparatus. G is an aneurism-needle.

NARCOTISING ANIMALS.—Narcotics cannot be given in all cases to animals on which we experiment, as their action must to a certain extent complicate that of the drug which we wish to investigate. We cannot use them when we are observing what are the general symptoms which a medicine produces. But, when we are investigating its action on particular organs, we may often use them, not only with safety, but with advantage, when they have no action on the particular organ which we are studying, or so little that its disturbing influence is more than compensated by the diminished muscular action, and consequent ease in performing the experiment, which narcotics produce.

It is almost unnecessary to say that, in all cases which admit of it, narcotics should be used, as we have no right to inflict any unnecessary pain, although we may be justified in taking the lives of the lower animals in order to preserve the more valuable life of man, either by supplying him with food by means of those killed in the slaughter-house, or by obtaining the knowledge which shall enable us to cure disease by means of those killed in our experiments. The narcotics which we use are opium and chloral. Chloroform is inadmissible, as its administration generally seems to cause dogs more pain than the experiment itself, and rabbits are very easily killed by it.

A convenient form of giving chloral is a solution containing half a grain in 1 minim or 1 *gramme* in two cubic *centimètres* of water. The dose for a frog is 2 to 5 *centigrammes*, or about 1 to 5 drops. The dose for guinea-pigs is about 12 minims of this solution for an animal half a pound weight; and more or less may be given, according to the weight of the animal, 18 minims being given to one weighing three-quarters of a pound, and 24 to one weighing a pound. About the same proportion of dose to weight may be employed for rabbits.

Opium may be given in the form of laudanum, or of solution of acetate or hydrochlorate of morphia. Much as it is used, the proper dose for different animals has not been exactly determined. We do not often employ it to narcotise guinea-pigs or rabbits, but frequently for dogs. The dose for a medium sized dog is about 40 minims or 2½ cubic *centimètres* of laudanum, or 2 drachms of liquor morphiæ, which is equal to 1 grain or 5 *centigrammes* of morphia. This dose is for injection into a vein: when injected subcutaneously, rather more should be given. If the dog be above or below middle size, the dose must be proportionately increased or diminished. We must be careful not to give too much opium to old dogs, or they will die. Opium is preferred by some to morphia, as producing more certain narcosis, and being less likely to produce the excitement and hyperæsthesia which sometimes follow the administration of morphia.

When we wish to render the animal absolutely motionless, or to observe what effect any drug will produce after the motor nerves have been paralysed, we give curare. Small doses of this remarkable substance paralyse the motor nerves of muscles, but leave the vagi and vaso-motor nerves unaffected. Large doses of it seem also to cause paralysis of the vagi. It affects the blood-pressure to a certain extent, moderate doses contracting the vessels and raising the pressure, while large ones lower it. The dose of curare for a frog is about 1 to 5 drops or more of a solution of 1 part in 1000. The dose varies with the size of the frog and the purpose for which we wish it. If we wish to observe the circulation microscopically, we must not give too large a dose, or the heart may stop. To rabbits, ½ to 1 cubic *centimètre* or 8 to 15 minims, and to dogs, 4 to 6 cubic *centimètres* or 1 to 2 drachms, of such a solution, may be given.*

Definite rules cannot be laid down as to the experiments in which narcotics may or may not be used. The experimenter himself must judge in each case whether their action is likely to disturb that of the drug to be experimented on or not. For this purpose, he must know the action which the narcotics themselves produce; and I will, therefore, mention in a few words what that of each is.

ACTION OF NARCOTICS.—Chloral acts on the brain, producing deep sleep, during which there is no sensation or voluntary motion. The reflex function of the spinal cord is first increased and then diminished in frogs; in guinea-pigs and rabbits, it is diminished for thermal irritations, but not for tactile ones—pinching producing reflex action, but burning or pricking none. It leaves the motor nerves, vagus, and muscles unaffected; but diminishes the activity of the respiratory nervous centre, rendering the breathing slow; and of the cardiac ganglia, somewhat weakening the heart. It lessens the blood-pressure and temperature, probably by dilating the vessels at the surface as the ear of a rabbit becomes hot and its vessels dilated, while the general temperature is falling.(27)

Opium is a mixture of several alkaloids, some of which are purely narcotic, while others produce tetanus, just like strychnia, and others partake of both characters. This is the case with morphia, in which, however, the narcotic qualities predominate. In small doses it first slightly increases, and then diminishes the irritability of motor and sensory nerves, and the reflex action of the cord, the irritability of the vagus (ends and central roots) and the musculo-motor apparatus of the heart, and the temperature. If the dose be large, those functions may be at once lessened. The blood-pressure varies, but is generally raised.(28)

The advantage of giving either a narcotic or the drug to be investigated by injection into a vein rather than subcutaneously is, that the action is immediate, and we know that the whole of the dose has taken effect; whereas, after subcutaneous injection, a part may remain for some time in the cellular tissue before it enters the blood and becomes active. The most convenient vein is the external jugular. In dogs, however, it is sometimes more convenient to inject the narcotic into a vein which runs obliquely across the outside of the hind knee-joint. Before injecting, we must introduce a cannula into the vein; and the introduction of a cannula into a vessel is an operation on the proper performance of which the success of many an experiment depends.

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* Curare may be obtained from Messrs. Hopkin and Williams, New Cavendish Street, London; or from Bruckner and Lampe, Leipzig.

INTRODUCTION OF CANNULÆ INTO VESSELS.—First, the hair must be cleanly clipped or shaved away, and loose hairs removed by a moist sponge. The skin, subcutaneous cellular tissue, and cutaneous muscles, are divided with a scalpel, and any bleeding vessels are twisted or ligatured. If the vessel lie deep, the muscles are separated from each other by the finger of the operator, or by a blunt aneurism-needle, and any unyielding connective tissue may be cut by a pair of scissors. That surrounding the vessel itself should be separated from it by the aneurism needle. A closed pair of forceps may be pushed under the vessel and then opened. This both raises it from its bed, and lays bare a considerable part of its course. A couple of ligatures are now caught between the jaws of the forceps and drawn through. The proximal end of the exposed part of the vessel is now compressed by a pair of smooth-pointed bulldog-forceps, or a ligature laid in a simple slipknot; one ligature is firmly tied round the distal end, and the second ligature is tied in a loop round the middle, but is not drawn tight. A small piece of calling card, about an eighth of an inch broad, is then slipped under the vessel, so that it may rest on it and remain steady; its walls are then snipped by a sharp-pointed pair of scissors just on the distal side of the loop. The finder, or aneurism-needle, may be introduced so as to make the opening more distinct, and, if necessary, this may be enlarged by the points of the forceps being introduced, and then separated. One lip of the divided vessel is seized by the forceps, the cannula introduced, and the loop drawn tight over it so as to tie it firmly into the vessel. The cannula is then filled by a small glass pipette with the fluid to be injected, the syringe is fitted on, the bulldog forceps removed, and the requisite amount injected. The bulldogs are again put on, and the syringe removed.

INJECTION OF FLUIDS INTO VESSELS.—First, we prepare the solution to be injected in a test or a watch-glass, and see that the syringe is in working order. The most convenient is one for subcutaneous injection, with a glass barrel and a graduated piston. On the piston-rod a small nut screws up and down, so that it can be set to any figure on the rod, and thus prevents it from being any further pushed in, so as to allow the exact amount required to be given at once, but prevent the accidental injection of more than this amount. The end of the barrel must either fit directly into a cannula of the shape shown in fig. 3 C, or it may be adapted to a glass cannula by tying a small piece of India-rubber tubing to the cannula. The cannula is then introduced into the vessel as already described. A fine pipette must be at hand, made by drawing a piece of glass tubing to a point, and by this the cannula, or cannulæ with the attached India-rubber tubing, must be carefully filled with the fluid, so that no air-bubbles remain. The syringe is then connected to it, the slip-knot of the ligature untied, or the bulldogs compressing the vessel in front of the cannula removed, and the necessary amount injected. The slip-knot is then re-tied, or the bulldogs replaced, if a second dose is to be given. If no more is to be injected, the vessel may be firmly ligatured.

DIVISION AND IRRITATION OF NERVES.—The nerve must be laid bare, and separated from the surrounding connective tissue in the same way as a vessel, especial care being taken never to seize the nerve itself with the forceps. Blood must be removed by a sponge squeezed quite dry, and the nerve must on no account be touched with water. If we wish to remove any adhering clot, or if the nerve happen to get dry through long exposure, it may be moistened with a little saliva or serum. A director is then pushed under the nerve, or we raise it up by a ligature passed below it, so as to secure the adjoining vessels from injury, and we then divide it by a pair of scissors. Very often we wish to have the nerve prepared for section some time before we actually divide it. We then pass the ligature under it and tie the two ends together, so as to prevent the ligature from being pulled from below the nerve, and thus form a loose loop by which we can at any moment raise and divide the nerve.

Nerves may be irritated by pinching, the application of strong saline solutions, or heat; but generally we use Pulvermacher's galvanic forceps, which are made of alternate wires of copper and zinc, and dipped in acetic acid, or, still oftener, the interrupted current from Du Bois Reymond's induction coil. The most convenient electrodes for this purpose consist of two wire points, about a quarter to half an inch long, and an eighth to a quarter of an inch apart. They may either be set in an ivory handle, or they may be simply fixed in a piece of glass tubing by means of cement or sealing-wax, or simply pushed through a piece of cork.

ARTIFICIAL RESPIRATION IN MAMMALS.—Artificial respiration is chiefly used to keep an animal alive after it has been poisoned with curare, for the purpose of rendering it perfectly still during an experiment; or after the thoracic cavity has been opened for observation or experiment on the viscera it contains. It is performed by introducing a cannula into the trachea, and inflating the lungs by means of a bellows connected with it by India-rubber tubing.

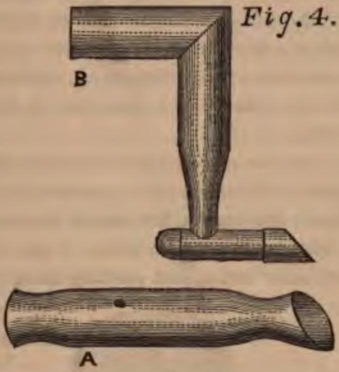


Fig. 4.

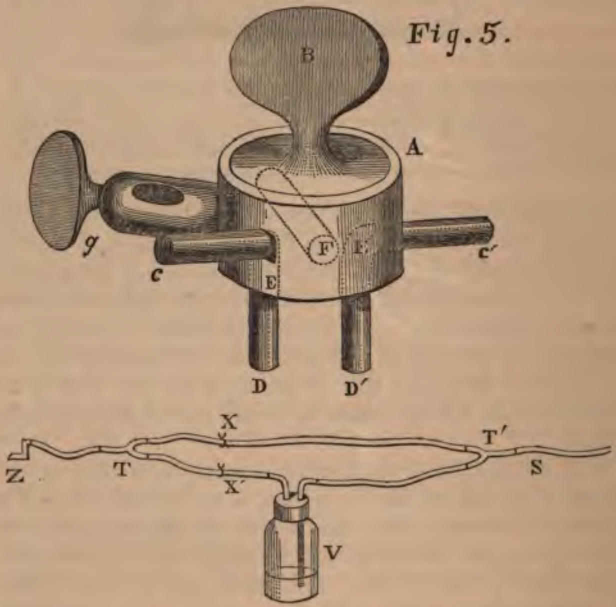
A is a glass cannula for artificial respiration, large enough for a small dog. A hole for the exit of expired air is seen in the side. B a metal one for a rabbit. The hole for expiration is at the top, and not visible in the figure. The lower part of the cannula can be turned round upon the upper at a joint about one-third of the way from the top, not marked in the figure. The tube which conveys air can thus be brought from the side instead of the front.

To introduce the cannula, an incision is made in the middle line below the cricoid cartilage through the skin and cutaneous muscles; the larger muscles lying along the side of the trachea are separated from it by an aneurism-needle or the handle of the knife, and a strong ligature is passed under it by an aneurism-needle or forceps, care being taken to avoid the veins which lie close to its posterior wall. A round or oval piece must then be cut out of the front of it by the scissors or knife, and the cannula introduced, and tied firmly in by the ligature.

When the knee-shaped metal cannula is used, it is advisable to push the heel of the cannula into the trachea, so that the tube lies quite in its lumen. After the cannula has been tied into the trachea, the ends of the ligature may be fastened round the upright bend of the knee, to ensure that it do not slip out. The bellows may be simply held in the hand, or fastened to the under side of a table by means of a piece of board screwed to its upper side and larger than the bellows itself, so that there is a rim of board all round. A few screws passed through this projecting rim into the under side of the table hold the bellows fast. A small pulley (one used for window-blinds will do) is then screwed into the under side of the table, and a cord passed over it. One end of the cord is fastened to a piece of board a foot and a half or two feet long, which serves as a treadle; and the other end to the under board of the bellows, so that it may be drawn up when the treadle is pressed down by the foot. A weight must be attached to the under board of the bellows, in order to draw it down again after it has been raised. The respiration is kept regular by depressing the treadle in accordance with the beat of a metronome set to beat the proper number in a minute.

The apparatus may be rendered more complete by the introduction between the bellows and trachea of a valve which will allow the air to pass readily towards the trachea, but hinder its return. Such a valve may be readily made by passing two pieces of glass tubing through the cork of a wide-mouthed bottle, and partially filling it with mercury or water. The tube nearest the bellows must descend nearly to the bottom of the bottle, while the other just passes through the cork. The air from the bellows passes easily through the mercury or water in

Fig. 5.



which the end of one tube dips; but any attempt to return simply raises the mercury in the tube. If water be used, the tube must be longer, so that it may contain a column of water sufficiently high to afford the necessary resistance to the return of the air. This sort of valve is termed Müller's valve. (Fig. 5, V.)

ARTIFICIAL RESPIRATION IN THE FROG.—Although the frog can live perfectly well for some time without breathing, it may be desirable in some experiments to employ artificial respiration. A cannula for this purpose is best made by heating the end of a glass tube about one-eighth of an inch in diameter (more or less, according to the size of the frog), and then suddenly pressing it down on a metal plate, so that a broad rim is formed round the end. The sides of the larynx are seized by two artery forceps, the cannula introduced, and tied firmly in. A Richardson's spray-producer, from which the tubes have been removed, is then connected to it and used as a bellows.

INTRODUCTION OF GASES OR VAPOURS INTO THE LUNGS.—Gases or vapours may be introduced into the lungs either by simple inhalation or by artificial respiration. For the inhalation of a gas, a conical bag of oilskin, India-rubber, or bladder, must be made to fit the snout of the animal, and connected with a bag, bladder, or gas-holder containing the gas. Or a tube may be put into the trachea and connected with the gas-holder.

For the inhalation of a vapour, a cone of strong paper or cardboard may be used, the wide end being put over the muzzle, and the liquid, the vapour of which is to be inhaled, dropped on a piece of blotting-paper and put on the small end. Or the whole cone may be made of blotting-paper.

Many different kinds of apparatus have been used for the artificial respiration of gases, among which may be mentioned the ingenious instrument of Thiry(29) and the beautiful respiration-pump of Ludwig. The simplest method probably is to have the gas in a bag, connected by means of the bottle or Müller's valve with the tracheal cannula. The gas may then be forced into the lung at intervals, by alternately compressing and relaxing the bag.

Air may be loaded with vapour of any kind of fluid before it is sent into the lungs, by either mixing the fluid with the water in the bottle-valve, or by emptying out the water and putting a little of the fluid alone on the bottom of the bottle. Pure air or air loaded with vapour may be sent into the lungs alternately by the arrangement shown in fig. 5. A stream of air is sent from the bellows through the India-rubber tube S, and divided into two by the T-tube T′. When the clip X is removed, and X′ put on, the air passes straight through to the tracheal cannula Z. If X be now put on, and X′ removed, the air passes through V, and becomes loaded with the vapour of any fluid placed in the bottle.

The alternation may be effected still more rapidly and conveniently by a stopcock which I have had made for this purpose. Two tubes, C and C′, pass from its sides, and two others, D and D′, from its bottom. The interior is perforated with three holes. Two of these, E and E′, are L-shaped, and one (F) passes straight through from side to side. When the handle B is in a line with C and C′, their lumen corresponds with that of the hole F, and air passes straight through. When B is transverse, the hole E corresponds with C and D, and E′ with C or D′, so that air passing in through C′ passes down through D′, and may pass up through D and out at C. When B is neither in a line with C nor yet transverse, but half-way between, the holes in the interior do not correspond with those on the exterior of the stopcock, and no air can pass at all, and it may thus be used for experiments on asphyxia. When such experiments are made, the hole in the tracheal cannula must be carefully stopped with white wax. By means of the screw G the stopcock may be fastened to the rod E of the rabbit-hold in fig. 1. The tubes D and D′ may either be attached by pieces of India-rubber tubing to tubes of a bottle such as V, or they may be themselves passed through the cork and a small piece of glass-tubing long enough to reach the bottom of the bottle attached to D′. By then simply turning the stopcock, pure air may be passed direct to the lungs through C′, F, and C, or it may be loaded with vapour by passing it through D′ into the bottle, and then up through D and C to the lungs.

III.—ARTIFICIAL CIRCULATION : INVESTIGATION OF BLOOD-PRESSURE.

Artificial Circulation of Blood.—Circulation of Warm and of Cold Blood.—Fever.—Mode of Conducting Artificial Circulation.—Application of this Method to Pharmacological Investigations.—Schema of the Circulation.—Circulation in the Living Body.—Importance of the Arterial Elasticity.—Arterial Tension or Blood-Pressure.—Oscillations in it produced by the Heart and Respiration.—Causes of Variation in the Blood-Pressure.—Influence of Nerves upon it.—Cardiac Ganglia.—Inhibitory Nerves of Heart.—Quickening Nerves of Heart. Vaso-motor Nerves.—Vaso-inhibitory Nerves.—Action of Counter-irritants.—Tabular View of the Causes of altered Pulse-Rate and Blood-Pressure.—Application of this to Pathology.—Experimental Examination of Blood-Pressure.—Forms of Manometer.—Kymographion.—Mode of Using the Kymographion.—Reduction of the Kymographion Tracings.—Mode of Recording Experiments.—Graphic Method of Representing Experiments.

ARTIFICIAL CIRCULATION OF BLOOD.—A constant supply of arterial blood to all parts of the body is necessary to preserve their vitality ; and if the supply to any part be cut off by stopping its circulation, that part will die. Thus, if the circulation be stopped in an arm or leg by tying its arteries, or through their becoming plugged by emboli, mortification, or death of the part, ensues ; and if the heart cease to beat, and the circulation be thus stopped in all parts of the body, they all die. But, if we supply arterial blood artificially to any one part, we may keep it alive at least for a certain time after the rest of the animal is dead ; and the muscles may be made to contract,(30) the lungs to excrete carbonic acid,(30) the lymphatics to pour forth lymph,(31) and the excised liver to secrete bile,(32) for hours after the rest of the animal has been consigned to the dust-bin.

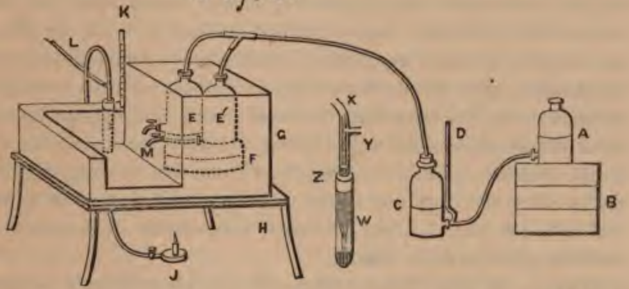
CIRCULATION OF WARM AND COLD BLOOD.—For this purpose, blood may be used either at the temperature of the room or of the body ; but these have not exactly the same effect, and experiments made with blood at one temperature must not be compared indiscriminately with those made with blood at another. Professor Ludwig, to whom we owe this method, has discovered by its means the curious fact that the muscles of a warm-blooded animal may be artificially endowed with the properties of those of a cold-blooded one. (33) Those of a frog or other cold-blooded animal retain their irritability, and contract, when stimulated, for a long time after they have been removed from the body; while those of warm-blooded animals quickly lose theirs, and will no longer contract on the application of a stimulus, no matter how powerful it may be. But if the muscle of the warm-blooded animal be quickly cooled by passing a stream of *cold* blood through its vessels immediately after it has been excised from the body, and before it is stimulated, it will retain its irritability for a long time, and respond to stimuli applied again and again, like that of the cold-blooded frog.

FEVER.—In the same way, by supplying the heart of a mammal with cold blood, it may be made to resemble that of a frog or turtle;(33) while, on the other hand, if the heart of a frog be supplied with warm blood, it will become like that of a mammal; and, if the temperature be still further raised, the quick and weak beats of fever are produced. (34)

MODE OF CONDUCTING ARTIFICIAL CIRCULATION.—When we wish to pass blood, at the ordinary temperature of the room in which we are working, through any organ, we defibrinate the blood of the animal itself from which the organ has been obtained, or the blood of an animal of the same species; dilute it somewhat with salt solution of 1 per cent.;(35) and put it into a flask with two necks, one of which is near the bottom of the flask, as seen at A, Fig. 6. We then introduce a cannula into the principal artery of the organ, and ligature, if necessary, the smaller arteries and branches; fill it carefully with blood by means of a fine pipette, so that no air-bubble remains in it, and connect it with the lower neck of the flask. By then simply raising the flask, the blood flows out of it through the cannula into the vessels, and out again by the veins, from which it may be collected, shaken with air, and used over again. As the lips of the divided veins are sometimes apt to fall together and hinder the exit of blood, it is advisable to put a cannula into them as well; and great care must be paid to the adjustment of these, in order that they may be fairly in a line with the lumen of the vein, and not form an angle with it, which would present an obstruction to the flow of blood from it.

For the purpose of passing a stream of blood at the temperature of the body, we use the same apparatus; but the flask containing blood (E, Fig. 6) is then placed in a water-bath, kept constantly heated to 98 deg. F. As this prevents us from conveniently raising the flask high enough to obtain the pressure required to carry on the circulation, we supply the want by compressing the air in the upper half of the flask, E, by means of two other bottles, A and C, containing mercury or water. On raising A, the fluid which it contains runs into C, and compresses the air in its upper half; and, as this communicates with E by an India-rubber tube, the pressure is freely transmitted to it, and exerted on the surface of the blood which it contains.

Fig. 6.



A and C. Bottles containing mercury or water. B. Wooden blocks, by which A may be raised to the required height. If water be used, it is easier to suspend it from a pulley in the ceiling, so as to get sufficient pressure. D is a manometer, to estimate the pressure in C and E. E is a bottle containing blood. F is a small stand to raise the bottle E from the bottom of G, as it is otherwise apt to become too warm, and the bottom of the bottle cracks, or the blood is decomposed. G. A tin water-bath. At one side of it, is a trough with hollow sides, into which the warm water freely passes, and in which the organ to be experimented on may be laid. H is an iron stand supporting G. I is a Mitscherlich's burner. K is a thermometer, by which the temperature of the water-bath is examined. L. Bunsen's gas regulator, as modified by Geissler. This apparatus consists of a wide glass tube W, divided into two parts by a septum, from the middle of which a tube runs down nearly to the end of W. The upper part is filled with mercury, which, of course, runs down the inner tube, and fills the bottom of W, compressing the air in it. A perforated cork Z is then put into the upper part of W, and the tube Y pushed through the hole in its centre. Inside Y, and shorter than it, is a second tube X, and the two are sealed to one another at their upper ends. The tube Y is then connected to a gas pipe, and X to Mitscherlich's burner, by India-rubber tubing. So long as Y is not pushed so deeply into W that the point of X dips into the mercury, the gas enters through Y, passes down between Y and X, comes up again through X, and goes to the burner. The apparatus is now set by dipping it into the water-bath, and heating the water to 98 deg , or any other temperature desired, and then pushing Y down till the point of X is just covered by the mercury. The passage of gas through it is at once stopped, and the flame would go out, were it not that a very small hole in the side of X admits just enough gas to keep it alive. As the flame gets low, the temperature of the water-bath above it diminishes: the air and mercury in W contract and leave the end of X open, so that the gas again passes freely to the burner, and the flame becomes larger. The water-bath now regains its former temperature, the air and mercury expand, the end of X is again closed, and again the flame becomes small. By this apparatus, a water-bath may be kept for a very long time without varying more than half a degree.

APPLICATION OF THIS METHOD TO PHARMACOLOGICAL INVESTIGATIONS.—Besides its use in the experiments of Ludwig and his pupils on the secretion of bile and the formation of lymph, this method has been used by Cyon to show that urea is formed in the liver ;(36) but, so far as I know, no experiments on the action of medicines have yet been made by its means. It may seem, then, a strange thing that I should mention, in a course of experimental pharmacology, a mode of research which as yet has only been tried in physiology; but the good service it has already done the physiologist, and the splendid promise it gives to us, are, I think, a sufficient excuse. For we can thus take two similar organs, or two parts of the same organ, and supply them with the same blood, at the same temperature and the same pressure—in short, we may put them under exactly the same external conditions; but to the blood supplying the one we may add any drug whose action on the organ we wish to test. We can analyse the blood flowing into, and that flowing from, the substance of the organs before and after the experiment, the lymph produced, or the secretion poured forth; and by comparing the results when the drug was added with those obtained when it was withheld, we may, I think, gain such a knowledge of its action as could be got in no other way.

SCHEMA OF THE CIRCULATION.—In the living body, a constant stream of blood is kept up in the vessels, in exactly the same way that a constant current of air is produced in Richardson's spray-apparatus. By removing the glass or metal tube from one of these, and attaching a nozzle with a small stopcock to the India-rubber tube in its stead, we obtain a very good schema of the circulation ; and, by imitating on it the changes which occur in the heart and vessels, we may form a much clearer idea of them than we could otherwise do. The India-rubber ball will represent the heart; the elastic bag, surrounded by netting, will represent the elastic aorta and larger arteries ; and the stopcock, which regulates the size of the aperture through which the air escapes, will represent the small arteries and capillaries, whose contraction or dilatation regulates the flow of blood from the arteries into the veins. If we turn the stopcock so as to present some resistance to the escape of air, and then compress the India-rubber ball, very little air will issue from the stopcock even while we are squeezing the ball ; the greater part of it goes to distend the bag ; and, when we cease to compress the ball, no air at all comes out from the stopcock. At the next squeeze, the bag becomes a little more distended ; and a little air issues from the stopcock, not only while we are compressing the ball, but even when we relax our grasp. At each squeeze of the ball, the elastic bag becomes tighter, till it is so tense, and contracts so strongly on the air inside, that it can press all the extra amount of air forced into it when the ball was compressed, out through the stopcock, during the time when the ball is relaxed. When this is the case, every time we squeeze the ball we see the bag become a little fuller, and air issue more quickly from the nozzle. At each relaxation, while the ball is refilling, the bag gets a little slacker, and the air passes out of the nozzle a little more slowly, but never stops entirely. During the time the ball is filling, the valves between it and the bag and nozzle are closed, and cut it off from any connexion with them. All this time, then, the stream of air from the nozzle must be entirely independent of the ball; it is produced by the contraction of the elastic bag, and by it alone. The bag may be stretched, and the tension of its walls increased in consequence, in two ways: first, by working the ball more quickly; second, by lessening the opening of the nozzle, and thus hindering the passage of air through it. One trial will, I think, be enough to show you how much easier it is to alter the pressure by changing the size of the nozzle than by any alteration in the working of the ball, and thus convince you that alterations in blood-pressure probably depend much more on alterations in the lumen of the small arteries than on changes in the action of the heart.

But our schema, as it at present exists, is not a perfect representation of the heart and vessels; for it draws its air from an inexhaustible reservoir, the atmosphere, and is not obliged each time to use that amount alone which it had previously driven through the nozzle; while the heart can only use the blood which has been forced by it through the capillaries and returned to it by the veins. In order to make our schema complete, we must connect its two ends by tying them into a bladder or large thin caoutchouc bag (such as is used, after inflation, as a toy for children), so that the air shall pass into it from the nozzle and be sucked out of it by the elastic ball. This will represent the veins. If we then repeat the experiment just described, we shall find that, when we begin to work the ball and stretch the elastic bag representing the arteries, the bladder, representing the veins, becomes empty and collapsed; and just in proportion as we fill the bag do we empty the bladder. If we now stop, the air will gradually escape from the bag to the bladder, till both are equally filled as they were at first.

CIRCULATION IN THE LIVING BODY.—The phenomena of the circulation in the heart and vessels are very much the same as in the spray-producer. When the heart stands still (as when the vagus is strongly galvanised), the blood flows from the arteries into the veins till they are nearly full and the pressure inside both is about the same. (37) If the heart now begin to beat, it forces blood into the elastic aorta and arteries at each systole, and distends them, just like the elastic bag of the spray-producer; while at the same time it takes blood from the veins, and they become empty in proportion as the arteries become full. At every diastole, the elasticity of the distended aorta causes it to contract on the blood it contains, and keeps it flowing on through the capillaries till another systole occurs. During the diastole, the heart is completely shut off from the aorta by the sigmoid valves (just as the ball of the schema was shut off from the elastic bag), and the blood is kept flowing during this time by the elastic contraction of the aorta and large arteries. In general, the diastole is longer than the systole; so that for the greater part the circulation is carried on by the elasticity of the arteries, and not directly by the heart. The arteries become distended by the heart, just as the elastic bag was by the ball, and press more and more on the blood in them (so that it would spout higher and higher, if one of them were cut), till they are able during the diastole to press the same amount of blood through the capillaries into the veins as had been pumped into them during the systole. The more these are stretched, the greater is the pressure they exert on the blood they contain; and the amount of this is termed the *arterial tension* or *blood-pressure.* These two terms mean the same thing, and we use one or other just as the fancy strikes us. At each systole, the fresh supply of blood pumped in by the heart stretches them more; that is, the arterial tension rises. During each diastole, the blood escapes into the wide and dilatable veins, and the arteries become relaxed; that is, the arterial tension falls.

Besides the oscillations which take place in the blood-pressure at each beat of the heart, a rise and fall in the form of a long wave occurs at each respiration. The wave begins to rise just after inspiration has begun, reaches its maximum just after the beginning of expiration, and then begins to fall again till a new wave succeeds it. (38) The heart-beats are generally quicker during inspiration, and slower during expiration.

The blood-pressure thus oscillates up and down at each heart-beat and rises and falls with each respiration, and the average between the highest and lowest points is called the mean arterial tension or mean blood-pressure.

CAUSES OF VARIATION IN THE BLOOD-PRESSURE.—The pressure of blood in the arteries depends on two circumstances: first, the amount of blood pumped into them in a given time; and second, on the amount that flows out of them into the veins in the same time. If more be pumped in, or if less flow out, it will rise; if less be pumped in, or if more flow out, it will fall. It may, therefore, be raised—1. By the heart beating more quickly; 2. By a larger amount of blood being sent into the aorta at each beat; 3. By contraction of the small vessels. It may be lowered—1. By the heart beating more slowly; 2. By the heart sending out less blood at each beat; 3. By dilatation of the small vessels, allowing the blood to flow more quickly into the veins; 4. By contraction of the pulmonary vessels, or obstruction to the passage of blood through them.

The influence on the pressure exerted by the amount of blood sent out by the heart at each beat, and by the number of beats, to a certain extent, though by no means completely, counteract each other; for, when the heart is going quickly, it has not time to fill completely, and so sends out little blood at each beat; but, when going slowly, it becomes quite full during each diastole, and sends out a larger quantity of blood at each contraction.

It must be remembered that we measure the blood-pressure in the systemic arteries; and, before the blood can get into them from the veins, it must come through the pulmonary vessels. Any contraction of the lumen of these vessels, by lessening the entrance of blood into the systemic arteries, will cause the pressure in them to fall.

INFLUENCE OF NERVES ON BLOOD-PRESSURE.—Both the quickness of the heart's beat and the contraction of the arteries are regulated by the nervous system; and it is generally by acting on different parts of it that drugs alter the blood-pressure, though they may also do so by acting on the muscular walls of the heart and arteries themselves. The parts of the nervous system chiefly concerned in regulating the circulation are:

I. The *cardiac ganglia* which lie in the walls of the heart, and are, in all probability, the cause of its rhythmical action.

II. *Inhibitory nerves*, which render the heart's action slow, and, if irritated very strongly, may stop its beating altogether, and produce still-stand in *diastole*. The inhibitory fibres have their origin or roots in the medulla, and proceed in the vagi to the heart. In man and in dogs, they are normally in constant action; and, after they are cut or paralysed, the heart beats in the dog three or four times as quickly, and in man twice as quickly, as before. In rabbits and cats, they act less, and their division only makes the heart go one-half or one-fourth faster. (39) A drug may irritate them, and render the heart's action slow—

1. By acting *directly* on (*a*) their roots in the medulla, (*b*) their fibres, (*c*) their ends in the heart;

2. Indirectly, through its action on other parts, producing (*a*) increased blood-pressure, or (*b*) accumulation of carbonic acid in the blood, both of which act as irritants to the vagus-roots;(40)

3. Reflexly, through irritation of sensory nerves,(41) irritation of the intestines,(42) of the sympathetic nerve,(43) of the depressor,(44) or of the vagus of the other side.(45) Reflex irritation is only likely to be caused by drugs having a powerful local action.

Drugs may also paralyse the inhibitory fibres, and thus quicken the heart.

III. *Quickening Nerves.* These belong to the sympathetic system. They have their origin in the brain or medulla, pass down through the cervical part of the spinal cord to the last cervical and first dorsal ganglion (which are often united), and thence through the third branch of the ganglion to the heart.(46) Quickening fibres are said by some to run also in the cervical part of the sympathetic cord.(47) Unlike the vagus, the quickening nerves are not normally in constant action.(48) They may be irritated—

1. By the direct action of drugs upon them.

2. Indirectly by the drugs producing a diminished blood-pressure, which acts as a stimulus to them.(49)

IV. *Vaso-motor Nerves*, which cause the smaller arteries, and probably also the capillaries, to contract. These belong to the sympathetic system; and the most important of them are the splanchnics, which produce contraction of the intestinal vessels. As these vessels can, under certain circumstances, hold all the blood in the body, the influence of the splanchnics over the blood-pressure is very great;(50) and division of these can lower it, or stimulation of them increase it very much. The centre of the whole vaso-motor system, however, seems to be in the medulla oblongata;(51) and it is generally in constant action, keeping up a certain amount of contraction or tone in these vessels. Its activity may be increased, and the vessels made to contract—

1. By direct irritation of the centre.

2. By reflex irritation through (*a*) the cervical sympathetic(52), (*b*) the vagus, when the brain is intact, and the animal not narcotised(53), (*c*) sensory nerves.(54) When the medulla is separated from the rest of the body by dividing the spinal cord at the atlas, it can, of course, no longer exert any influence over the vessels; and they consequently become dilated throughout the whole body, and the blood-pressure sinks very low. If the lower end of the divided cord be then irritated,

the vaso-motor nerves which pass through it from the medulla to the body are stimulated, and the blood-pressure rises.

V. *Vaso-inhibitory nerves.* Irritation of these nerves is conducted to the vaso-motor centres, and acts on them in such a way as to cause a reflex dilatation of the small vessels, either (1) throughout the whole body, or (2) in one particular part of it.

1. The chief nerve which causes dilatation throughout the whole body is one which runs from the heart to the medulla, and is called, from its power of diminishing blood-pressure, the depressor nerve.(55) Its fibres seem to be included in the vagus in the dog; but in the rabbit it generally runs separate from the heart to the level of the thyroid cartilage; here it divides into two so-called roots, one root going to the superior laryngeal, and the other to the vagus nerve. These are generally called roots, though, as the nerve conveys impressions *from* the heart *to* the brain, they are, physiologically, really branches. There seem to be also depressor fibres in the vagus itself;(56) but this nerve contains fibres of many kinds, and, among others, some which cause contraction of the vessels and rise of blood-pressure—hence called pressor-fibres.(57) The former seem to act on the vaso-motor system through the medulla itself, while the latter affect it through a centre in the brain, so that, when the brain is perfect, irritation of the central end of the vagus causes increased contraction of the vessels and raised blood-pressure; but, when the brain is removed or its functions abolished by opium, it causes dilatation of vessels and diminished pressure.(58)

2. When a sensory nerve is irritated, the action of the vaso-motor centre is suspended in the part supplied by the nerve, and in those which immediately adjoin it, so that their vessels become dilated, while at the same time contraction of the vessels in other parts of the body is produced. The blood-pressure is thus increased generally, and produces in the locally dilated vessels a very rapid stream of blood. This fact was first discovered, and its importance in therapeutics indicated, by Ludwig and Lovèn.(59)

ACTION OF COUNTERIRRITANTS.—The application of an irritant, whether mechanical, chemical, or thermal, injures the tissues of the part to which it is applied; and what better means of removing the injury and restoring health could be imagined than a copious supply of blood, and the removal of every hindrance to its free flow which contraction of the vessels might present?

Experiments are still wanting to decide how far the vascular dilatation will extend in the neighbourhood of the irritated part when more or less powerful irritants are applied, or which the vessels are (if any) which especially contract, when certain others dilate; so that at present, when we apply a mustard plaster to the chest to relieve bronchitis, we are unable to say with certainty whether the relief is due to a more full flow of blood through the vessels of the bronchi, or to contraction of their lumen diminishing congestion, or (though this is unlikely) to some unknown action independent of the vessels altogether. The experiments of Sinitzin, however (detailed by a recent writer in the BRITISH MEDICAL JOURNAL, 1871, p. 535), which show that ulcers of the cornea, eyelids, and lips, occurring after division of the fifth nerve, rapidly heal when dilatation of the vessels of these parts is produced by extirpation of the superior cervical ganglion, render it in the highest degree probable that it is to the increased flow of blood that healing is due. (60) As a general rule, too, the vascular dilatation seems to extend more widely the stronger the irritant applied; and we may thus see how a strong irritant, or one applied over a large extent of surface, may prove beneficial in a deep-seated inflammation when a weak one or one applied to a small surface has no effect.

For convenience of reference, I have put together the causes of alteration in the blood-pressure in the following table.

Causes of Alterations in Blood-pressure and Pulse-rate.

Blood-pressure may be diminished.	By slow action of the heart.	Irritation of vagus-roots.	Directly, by the action of the drug on them. Indirectly, by increased blood-pressure. ,, by accumulation of CO^2 in the blood. Reflexly, by irritation of some other nerve.
		Irritation of vagus-fibres?	
		Irritation of vagus-ends in the heart.	
		Increased excitability of vagus-ends in the heart.	
		Paralysis of sympathetic ends in the heart?	
		Weakness of the heart.	Paralysis of the cardiac ganglia. Paralysis of the cardiac muscular fibres.
	By smallness in the amount of blood sent into the heart at each systole.	Weakness of the heart. Contraction of the pulmonary vessels. Great dilatation of the venous system.	
	By dilatation of the small arteries.	Paralysis of the vaso-motor centre.	Direct, by the action of the drug. Reflex, through the depressor. Reflex, through vagus and sensory nerves, when brain is removed or animal poisoned by opium. In operations by division of cord or of splanchnics.
		Paralysis of the arterial walls.	
Blood-pressure may be increased.	By quick action of heart.	Paralysis of vagus-roots. Paralysis of vagus-fibres. Paralysis of vagus-ends in heart.	
		Stimulation of sympathetic roots.	Directly. Indirectly, by lowered blood-pressure.
		Stimulation of sympathetic fibres? Stimulation of sympathetic ends in heart?	
		Stimulation of the cardiac ganglia.	Directly. Indirectly, by causing increased temperature of body.
	By larger amount of blood at each beat.		
	By contraction of small arteries.	Irritation of vaso-motor centre.	Direct. Indirectly, by accumulation of CO^2 in the blood. Reflex, through the cervical sympathetic. Reflex, through the vagus, when the brain is present and the animal is not narcotised. Reflex, through sensory nerves.
		Direct irritation of vascular walls.	In operations by irritation of the peripheral ends of the divided spinal cord or splanchnics.

APPLICATION TO PATHOLOGY.—The brief sketch of the circulation which I have given, will enable you to understand and appreciate the meaning of the changes produced in our circulation by any drug, and to explain the facts we may meet with in the course of an investigation. I may remind you that the alterations in the pulse-rate and blood-pressure which we meet with in disease, as well as those produced by drugs, are due to some one or other of the causes mentioned in the previous table; and whenever you meet with a quick, slow, weak, or irregular pulse, you must try to find out to which of these causes it is due, in order that you may be able to apply scientifically the proper remedy.

EXPERIMENTAL EXAMINATION OF BLOOD-PRESSURE: FORMS OF MANOMETER.—As the life and health of the body and of the organs comprising it depend on the supply of blood to them—and this, as we have already seen, is closely associated with the arterial pressure—the observation of the effects of drugs on it naturally forms one of the most important parts of an investigation into their action. The first to measure the blood-pressure was Hales, who simply connected a glass-tube with an artery, and noted the height to which the blood rose in it. Poiseuille improved upon this method by substituting a bent tube, partially filled with mercury, for the straight tube, and estimating the pressure from the difference in the level of the mercury in the two limbs. A solution of carbonate or bicarbonate of soda was introduced into the tube between the mercury and the blood in order to prevent its coagulation. The bent tube, partly filled with mercury, is called a hæmadynamometer, or, more generally, a manometer. The height of the mercury is read off from a scale fixed behind the tube. Usually both limbs of the tube are of equal diameter, and the blood-pressure is then ascertained by doubling the height of the mercury in one limb above zero and subtracting a fraction, which varies with the specific gravity of the solution of soda used. The height must be doubled, because the mercury descends as much below zero in the one limb as it rises above it in the other; and a fraction of the whole is subtracted for the additional weight of the column of soda solution, which enters one limb as the mercury rises in the other.

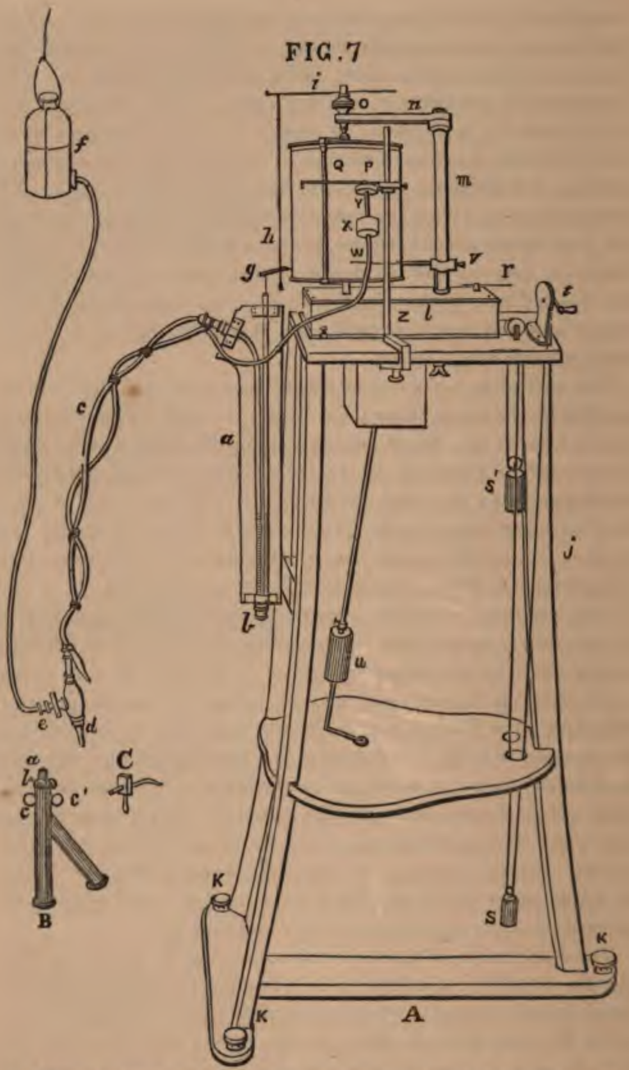
A very simple manometer, which will show the mean blood-pressure as well as the maximum and minimum between which it oscillates, may be made by passing two straight glass-tubes about sixteen inches long through the cork or India-rubber stopper of a small wide-mouthed bottle, and fixing behind them a graduated cardboard scale. The lower end of one tube must be nearly closed in the blow-pipe flame, and both pushed down till they almost touch the bottom of the bottle. A third bent tube is inserted into the stopper, reaching only to its under surface, and a piece of India-rubber tubing is attached to its upper end for the purpose of connecting it with the artery. Some mercury is then poured into the bottle, so as to stand a little above the ends of the tubes, and both it and the India-rubber tube are filled with a saturated solution of bicarbonate of soda and connected with the artery. The mercury rises and falls in the open tube with every pulsation; but in the one with the constricted end the resistance to its movement is so great that it can only rise and fall slowly, so that, before its upward oscillation has had time to show itself, its descent has begun, and *vice versâ*. The upward and downward oscillations thus balancing each other, the mean pressure only is shown.

The oscillations in the unconstricted tube are so rapid that it is impossible for the eye to follow them exactly; and this difficulty led Ludwig to conceive the idea of making them register themselves by means of a slender rod swimming on the surface of the mercury, and bearing at its upper end a pen which moved up and down on a piece of paper fixed on a revolving cylinder. The vertical height of the tracing thus produced showed the blood-pressure, while the horizontal distance from one point to another on it indicated the time between them.

This instrument is called a kymographion; and in devising it, Ludwig introduced for the first time into physiology that method of self-registration which is now generally applied to all kinds of vital phenomena, and has already done much to render our knowledge exact. That form of it which is used by Traube and made by Sauerwald of Berlin is shown in fig. 7. It consists of a metal cylinder (*p*) supported on a wooden frame (*j*), and caused to revolve at a steady rate by clockwork and pendulum (*l* and *u*). The manometer is fixed to the wooden frame and connected with the artery by tubing of lead and India-rubber. On the mercury in one limb floats a rod or swimmer of glass, to whose upper end is attached a glass pen (*g*), which registers the movements of the mercury on the revolving cylinder.

The disadvantage of the mercurial manometer is, that it does not give the true form or extent of the variations of blood-pressure, the inertia of the mercury causing it to oscillate above and below the true value. We may, however, obtain the true form of each oscillation along with the mean pressure by connecting the artery at the same time with the manometer and one of Marey's sphygmoscopes and levers (fig. 6, *x* and *y*) by means of a Y-tube, one end of which is connected to *d* and

FIG. 7



A. Ludwig's Kymographion. *a'*. The manometer. Instead of one simple bent glass tube, it consists of two tubes fixed on a piece of wood, and joined by a piece of metal *b*, which may be unscrewed for cleaning the tubes. *c* is a tube of soft lead, for connecting the manometer with the artery. One end of it is screwed to the manometer, and the other is attached to a stopcock *d*. *d* is a stopcock attached to *c*, and may be connected with the tube B in the artery by a piece of India-rubber tubing. It is bored in a T-shape, and is perforated in the centre by an additional perpendicular hole, into which is put a hollow plug *e*. *f* is a flask containing saturated solution of bicarbonate of soda, and connected by India-rubber tubing with *e*. When the clip on the India-rubber tube just above *e* is removed, and the stopcock turned longitudinally, soda solution will flow into *c* as well as out of *d*. By turning it transversely, the opening towards *c* may be closed, and soda will then only run out through *d*. This is done when we wish to wash out the cannula with soda without altering the level of the mercury in *a*. *g* is a glass pen attached to the top of a glass rod or swimmer, which rests on the surface of the mercury in *a*. *h* is a thread of unspun silk, with a small weight attached to it. It rests against the pen *g*, and keeps it constantly applied to the paper without impeding its movements. *i* is an iron wire, from which the thread *h* is suspended. *j* is the wooden frame bearing the clockwork and revolving cylinder. *k* are three screws to level the frame. *l* is the clockwork. *m* is an upright, and *n* a horizontal bar, which support a pivot *o*. *p* is a metal cylinder, which carries the paper. *q* is a small metal bar for holding the paper on the cylinder. It is hinged to the lower edge of the cylinder, and caught by a spring at its upper edge. It lies in a hollow in the cylinder, so that its outer surface does not project above it. When a new paper is to be put on, the spring catch at the upper end of *q* is raised, *q* pulled out, the old paper removed, and the edges of the new one placed under *q*. It is then pushed down, its upper end is caught by the spring, and the paper is securely held. *r* is a catch for stopping the movement of the clockwork. *s* and *s'* are two weights to drive the clockwork. *t* is a rack for winding up the weight *s'*. *u* is a pendulum, with a movable bob, to regulate the motion of the clockwork and cylinder. By moving the bob up or down, the motion may be made quicker or slower. *v* is a pencil stuck through a piece of cork, and fastened to the upright *m*, so as to draw a line on the paper at the same level as *g*, when there is no pressure on the mercury in the tube. The blood-pressure is estimated by the height of the curve traced by *g*, above the zero line thus drawn. *y* is one of Marey's tympana, which is supported on a movable rod *z*, and may be used for registering either the respiration or the form of the pulse-wave. It consists of a shallow cup of metal, over whose top a piece of India-rubber is tightly stretched. A metal tube passes into the interior of the cup, and a light lever lies over the upper surface of the India-rubber, and is firmly connected with it. When air is blown into the interior of the cup, the India-rubber bulges and raises the lever; when air is sucked out, it becomes depressed and draws the lever down. When used to register the respirations, it is simply connected with a tube in the trachea of the animal, or with a mask fitted before its nose. As the piece of India-rubber stretched over *y* is thin, it would be blown out, and perhaps burst, by the pressure, if we were to connect it directly with the artery. One of Marey's sphygmoscopes is, therefore, introduced between them, when we wish to measure the blood-pressure. The sphygmoscope consists of a little bag of strong India-rubber, enclosed in a piece of glass tubing, connected with the tympanum. The bag is filled with soda solution, and connected with the artery. Each time that the pressure rises in the artery, the bag becomes distended, and forces some of the air out of the glass tube into the tympanum, and raises the lever; and when the pressure diminishes, the bag collapses again, and the lever falls. *x* is a modification of this, designed by my friend Dr. Burdon Sanderson. Instead of a bag enclosed in a tube, it consists of a metal box, across the interior of which a septum of strong India-rubber is stretched. One side of the box is filled with soda solution, and connected with the artery; the other with air, and connected with the tympanum. *w* is a piece of lead tubing for connecting the sphygmoscope *x* with the tube in the artery.

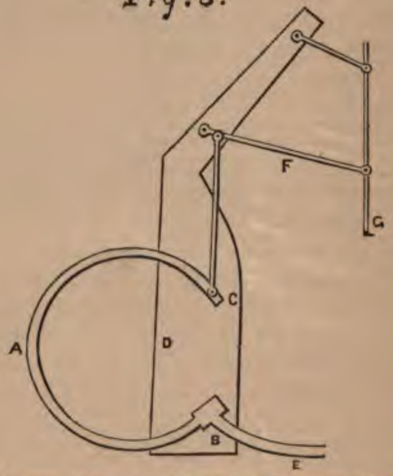
B is a forked tube of German silver or brass for connecting the artery with the kymographion. *a* is a cannula, which is inserted into an artery (see fig. 3A); *b* is a small ring soldered to it, by which it may be tied to the rings *e* on B, to prevent it from slipping off; *e* and *e* are two rings soldered to B. By means of ligatures passed through these, B may be fastened to the skin or hair of the animal to prevent its being displaced by any sudden movement. The oblique limb of B may be connected to A *d* alone by a piece of India-rubber tubing, or to both A *d* and A *w* at the same time by means of a Y glass tube and India-rubber tubing. Another piece of India-rubber tubing is attached to the straight limb *d*, and closed by a clamp or clip. When a clot forms, the clip is taken off, and the clot removed, the tube washed out by a stream of soda solution, and the clip again replaced.

C is the tracing-pen (see fig. 3B). It is stuck horizontally through a piece of cork: another small piece of glass tubing, about three-fourths of an inch long, closed at its upper end, and about one-twelfth of an inch in diameter, or just wide enough to admit the end of the swimmer, is stuck vertically into the same piece of cork

the other to *w*. In order to obtain the mean pressure we turn the stopcock (*e*), till on blowing through it only a slow rise and fall of the mercury can be produced, but no sudden oscillation. On then connecting it with the artery the mercurial column shows the mean pressure, while the sphygmoscopic lever registers each oscillation

Besides this form there are various others on the same principle, some of which have cylinders which wind off a continuous roll of paper from a bobbin, so that a tracing may be taken uninterruptedly for an hour or two without renewing the paper. In order to avoid the inconveniences of the mercurial manometer, Fick has constructed one (Fig. 8) in which the pressure is not measured by the movements of a column of mercury, but by those of a bent hollow tube (A) fixed at one end and

Fig. 8.



Fick's spring kymographion. A is a flat tube of German silver, fixed at one end B, to a piece of board D. The other end C is freely movable. E is a tube connecting A with the artery. F is a lever made of reed, connected to C. G is the writing point, moved up and down by F, and kept perpendicular by another short lever above. The tube A is filled with alcohol, and the tube E with a soda solution; and B is then connected with the artery. Whenever the pressure rises, the tube A tends to straighten itself, but it is firmly fixed at the end B, and so the end C alone moves upwards, and pushes up the lever F and the writing point G. Whenever the pressure relaxes, the tube bends back again to its original shape, and the point G consequently again descends. The tracing is taken by allowing G to rest against a revolving cylinder, covered with a piece of paper, which has been smoked either over a gas flame or a paraffin lamp.

free at the other. The tube is filled with alcohol, and its fixed end connected with an artery. At every rise of pressure this tube tends to straighten itself, and this motion of the free end is communicated by it to a lever (F) and writing-point (G), which records it on a smoked cylinder.

The advantage of this form of kymographion is, that it gives the exact form, duration, and extent, of each pressure-variation. Its disadvantage is, that the tracings it gives are on a small scale, so that it is not so well adapted for showing small oscillations of pressure like those at each heart-beat in the rabbit, although it answers admirably for dogs. Another disadvantage is, that the tracing must be taken on smoked paper, and this is more troublesome to manage than white paper and ink.

MODE OF USING THE KYMOGRAPHION.—The kymographion must first be rendered perfectly level by the screws, K K (fig. 7). The upper part of the outer tube of *a* and the tube *c*, the India-rubber tube connecting it with B, and B itself, are then filled with soda solution and the clip at *e* put on. A fresh sheet of paper is put on *p*, the pen (*g*) filled with ink, and the pencil (*v*) adjusted at the same level. A piece of cotton-thread should be drawn through the pen, so that the end projects just beyond the pen's point ; this makes the pen write better. The animal is next fixed, a vein exposed for injecting, the cannula (*a*) introduced into an artery in the way already described, the blood being prevented from entering the cannula by a clip placed on the artery. A drop of carbonate of soda solution is placed in the cannula (*a*), the tube (B) fitted into it and tied to it by a thread through the ears, *b* and *c*. Two other threads through *e* and *e* fasten the tube (B) to the skin or hair of the animal. The flask (*f*) is raised several feet above the apparatus, and the clip at *e* opened, so as to make the pressure in the manometer and tubes nearly equal to that of the blood in the vessels so as to prevent the blood from filling the tubes. It must not be greater, or the carbonate of soda will pass into the vessels and produce convulsions. The clip at *e* is then replaced and that on the artery removed, the cylinder set in motion, and a tracing of the normal blood-pressure taken.

The drug in solution is now injected into a vein and a fresh tracing taken. At the time the injection is begun a cross should be made on the tracing opposite the pen of the kymographion, and a O should be made when the injection is finished. The time at which these were made should be noted on a separate piece of paper, and afterwards copied on to the tracing itself. Instead of putting each time on a fresh piece of paper, two or three may often be taken on one paper by having two or three exactly similar glass pens of the form shown filled with inks of different colours. Each is stuck through a small piece of cork, and into the under side of the cork a small glass tube is put, which will just fit the top of the swimmer. By simply dropping the glass tube on the end of the swimmer the pen is in its place at once, and can be changed with great facility. A small sable brush may also be substituted for the glass pen.

After the experiment has gone on for some little time, a clot is apt to form in the cannula. When this is the case the clip must be replaced on the artery, the stopcock (*d*) turned transversely, so as to keep the mercury at the same height, the clip on the India-rubber tube of *d* B and at *e* A removed, and the tube washed out by a stream of carbonate of soda. Any clot in the cannula is removed by a spill of twisted paper, by a hog's bristle, or by a piece of whalebone. The whalebone-probes are most convenient, as they can be made of any size. A single jet of blood should now be allowed to escape from the artery, so as to make sure that there is no clot in it, the tube again washed out with carbonate of soda, the clips at *e* B and *e* A replaced, that on the artery removed, and the stopcock turned and tracings taken as before.

REDUCTION OF THE KYMOGRAPHION TRACINGS.—It is not only impossible to publish the tracings as they are taken from the kymographion for the benefit of others, but it is extremely difficult to draw any except very general conclusions from them for one's self. Before they can be of much use they must be reduced to tables, or, what is still better, the tables themselves may be graphically represented. In making the tables we must first fix the time at which the different parts of the tracing were made. The time when the tracing was begun and when the injection was made must be noted down at the time in a separate note-book, or, still better, on the tracing itself. In the first tracing it is convenient to take the time when the injection was made, as a starting-point from which to reckon the other periods.

Beginning at this point, then, we divide the abscissa or zero line into parts corresponding to five seconds each, or any other period we think convenient. If the circumference of the cylinder be sixty *millimètres*, and it revolve once in a minute, each five *millimètres* of paper will correspond to five seconds' revolution.

Secondly, we must ascertain the blood-pressure at different times. At the point where the injection took place, we draw from the tracing a perpendicular to the abscissa, and another, five, ten, or fifteen seconds further back. The mean pressure is most readily and exactly got by means of a planimeter; but, as this is an expensive instrument and possessed by few, we usually employ ruder methods. The first is to determine the square superficies of the irregular figure contained by the abscisse, the two perpendiculars, and the curve, and then divide it by the length of the abscissa: this gives the mean height of the pressure-curve. The size of the figure is ascertained by placing over it a piece of tracing-paper or glass ruled in square *millimètres*, and counting the number of squares contained in it. Volkmann cuts the figure exactly out in paper of uniform texture and weighs it. By then comparing its weight with that of a square of given size, the superficies of the figure is easily ascertained. The second method is still simpler, and, though not so exact, takes much less time, and is, therefore, frequently employed. It consists in drawing a straight line from one perpendicular to the other along the curve, so as to cut the pulse- and respiration-waves as nearly as possible in their middle, and leave as much of their surface above as below it. We then measure the height of this line above the abscissa, double it, and subtract from it the fraction of the whole, which represents the column of carbonate or bicarbonate of soda solution which entered one limb of the manometer and pressed on the mercury in it as the mercury rose in the other limb. For a solution of carbonate of specific gravity 1018, this fraction will be about $\frac{1}{27}$ of the whole.

Passing along the curve taken after the drug has been injected, we note the place where any change in pressure has occurred, and here we draw another perpendicular and proceed as before. Thirdly, we obtain the number of pulsations and respirations in a minute by counting the pulse- and respiration-waves between each two perpendiculars, and reckoning from the time between them what the rate of pulse or respiration will be in a minute. As the rate of both may change several times in a minute, and a calculation of this sort would lead to considerable error, we not unfrequently take fifteen seconds as the unit of time instead of a minute.

The way in which the numbers thus obtained may be tabulated, is shown by the following examples of supposititious experiments. These examples have been made by piecing together several experiments of Von Bezold, and show generally the action of atropine, but must not be regarded as accurate descriptions of any one experiment. Even when a continuous roll of paper is employed, instead of several separate pieces, it is often convenient to divide it by lines, and tabulate each part separately, just as when separate pieces of paper are used.

MODE OF RECORDING EXPERIMENTS.

Experiment I, November 5, 18 .

Young rabbit. Weight 1540 grammes. Jugular vein exposed and one cubic *centimètre* of tincture of opium, containing two *grammes* in twenty-five cubic *centimètres*, injected into it. Cannula in the left carotid. Animal otherwise uninjured.

	Time after injection.	Blood-pressure.	Pulse in 15s.	Respiration in 15s.	REMARKS.
TRACING I.					
Tracing begun 2.39. P.M.	..	78	60	23	2½ *milligrammes* of sulphate of atropine, dissolved in 2 cubic *centimètres* of water, injected into the jugular vein towards the heart.
Injection begun 2.39.15.	..	78	60	23	
" ended 2.39.25.	..	80	63	18	
At 2.39.35	10s.	83	65	19	
At 2.40.0	35s.	87	70	20	
TRACING II.					
At 2.40.30	1.5	92	92	22	

Experiment II, November 9, 18 .

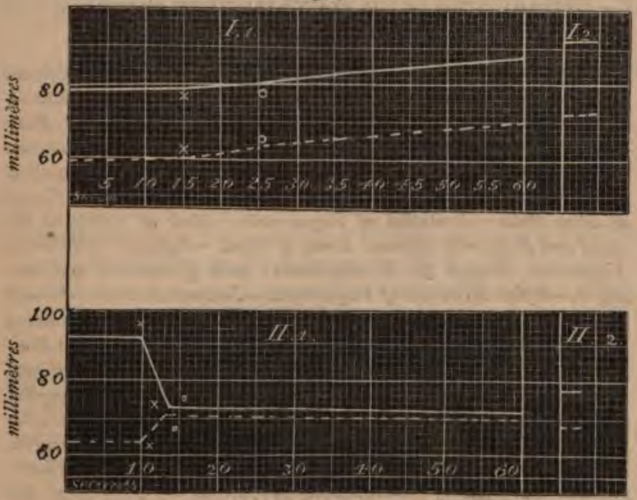
Old rabbit. Weight, 1764 *grammes*. Jugular vein exposed. Animal not narcotised. Cannula in the left carotid. Animal otherwise uninjured.

	Time after injection.	Blood-pressure.	Pulse in 15s.	Respiration in 15s.	REMARKS.
TRACING I.					
Tracing begun 3.50.0 P.M.	..	92	64	26	2 *centigrammes* of sulphate of atropine, dissolved in 2 cubic *centimètres* of water, injected into the jugular vein towards the heart.
Injection begun 3.50.10	..	92	64	26	
At 3.50.13	..	73	..	..	
Injection ended 3.53.15	..	73	70	24	
At 3.51.0	45s.	72	70	26	
TRACING II.					
At 3.58.0	7.45	78	68	25	

GRAPHIC METHOD OF REPRESENTING EXPERIMENTS.—In looking over a column of figures such as the tables we have now obtained, it is by no means easy to see at once what it really indicates; and it is still more difficult when we have to compare several tables together. For this reason it is of great advantage to convert the tables into curves, from which the result of any experiment can be learned at a glance, and the points of resemblance, or difference in the results of a whole series compared with the greatest ease.

To obtain these graphic curves, we reverse the process by which we formed our tables. We first take a piece of paper ruled in squares, and on it we draw a horizontal line or abscissa, and then a perpendicular to one or both ends, and number the spaces along both the abscissa and the perpendicular or ordinate. Those along the abscissa represent periods of time to which we may assign any value which is convenient, seconds, minutes, hours, or multiples of these. The numbers along the ordinate may represent blood-pressure, pulse-rate, number of respirations, or degrees of temperature; and we may describe curves representing all of these on the same paper, distinguishing them from one another by the use of different coloured inks. Fig. 9 represents graphically the tables of blood-pressure and pulse-rate in Experiments I and II. We begin the pressure-curve by making a dot on the first perpendicular, at a height corresponding to the number 78. Passing along horizontally from this for a space corresponding to fifteen seconds to the abscissa, we make another dot; and at ten seconds further, at a height corresponding to 80, we make a third dot, and so on. We then connect the dots by lines, and thus obtain the curves we wish.

Fig. 9.



IV.—DETERMINATION OF THE EXACT STRUCTURES THROUGH WHICH DRUGS AFFECT THE HEART AND VESSELS.

Comparison of the Effects of Drugs on different Animals in different Doses.—Mode of determining the Exact Cause of Symptoms.—Mode of raising Blood-pressure.—Modes of counting the Beats of the Heart.—Causes of Quickened Pulse.—Direct Stimulation of the Sympathetic.—Stimulation of Cardiac Ganglia.—Paralysis of the Vagus-roots and Fibres, and of its ends in the Heart.—Causes of Slow Pulse.—Irritation of Vagus-roots.—Mode of supplying the Head and Body with different kinds of Blood.—Indirect Irritation of Vagus-roots through the Blood-pressure: mode of lowering and raising it.—Reflex Irritation of Vagus-roots.—Indirect Irritation through the Respiration.—Irritation of Vagus-fibres.—Increased Conducting Power of Fibres.—Stimulation of Vagus-ends.—Paralysis of the Sympathetic.—Paralysis of the Cardiac Ganglia.—Part of the Ganglionic Apparatus Affected.—Nervous System in the Heart.—Motor Ganglia.—Stimulating Ganglia.—Inhibitory Ganglia.—Connecting Apparatus.—Action of Drugs on the Inhibitory Apparatus—Nicotia, Muscaria.—Antagonism of Atropia and Physostigma: bearing of this on Therapeutics.—Paralysis of Co-ordinating Apparatus.—Paralysis of the Muscular Fibres of the Heart.—Blood-pressure: mode of determining whether changes in it are due to alterations in the Heart or Vessels.—Elimination of the Action of the Heart: Division of its Nerves.—Irritation of Vagus.—Ligature of Aorta.—Artificial Circulation; in Mammals, in the Frog.—Observation of Vessels.—Action on Vasomotor Centre; on Vascular Walls.—Influence of ths Action of Parts surrounding the Vessels upon them.—Action of the Pulmonary Circulation on the Blood-pressure.—Use of the Sphygmograph.

COMPARISON OF THE EFFECTS OF DRUGS.—Before proceeding to examine separately the different structures through which a drug may act on the blood-pressure, it is advisable to compare the effects which it produces on animals of different kinds, such as dogs and rabbits, as well as the action of larger and smaller doses on animals of the same kind. Continuing to take as an example the action of atropia, admirably investigated by Von Bezold, we find the following results.(61)

With a small dose of atropia injected into the jugular vein towards the heart:

The blood-pressure rises in both rabbits and dogs:

The pulse becomes quick, rising in rabbits from 256 to 288; in dogs, from 80 to 240.

With a larger dose:

The blood-pressure, in both rabbits and dogs, falls at first and afterwards rises to the normal.

The pulse becomes quick in both.

With an additional dose:

The blood-pressure in rabbits falls very low as the poison reaches the heart; afterwards rises; and falls again below the normal.

The pulse becomes slower, and then quicker.

With a very large dose:

The blood-pressure sinks instantly in both rabbits and dogs.

The pulse in rabbits becomes slower and weaker, and then stops; in dogs, it becomes quick.

This comparison between the effects which atropia produces in different animals, and in large and small doses in the same animal, shows us that it sometimes raises and sometimes lowers the blood-pressure, but that it always quickens the pulse, except when a large quantity of the poison is introduced at once into the heart of the rabbit. On consulting the table already given (BRITISH MEDICAL JOURNAL, June 3rd, page 583), it will be seen that quickening of the heart may be due to stimulation of the sympathetic, either directly by the drug or indirectly by diminution of the blood-pressure; to stimulation of the cardiac ganglia; or to weakening or paralysis of the vagus. Any one of these conditions may cause quickened pulsation; and, in order to determine which of them really does it, we must test each one of them separately by farther experiment.

MODE OF DETERMINING THE EXACT CAUSE OF SYMPTOMS.—The plan which we follow is this: we suppose for the time being that the cause which we are testing is the true one, and consider what effects it will produce under certain conditions. We then supply these conditions experimentally, and see whether or not the results we obtain correspond with those which we should find if our supposition were correct. So in the present instance we first ask, Is the quickening of the pulse due to indirect stimulation of the sympathetic roots by diminished blood-pressure or not? We suppose for the moment that it really is so, and we consider that if we raise the blood-pressure we shall remove the cause of quickening and bring the pulse down again to its normal rate, We then proceed to raise the pressure, and see whether or not the pulse is rendered slow, as we expect it to be. In the case of atropia, a special experiment is not necessary for this purpose, as we have seen that small doses do not *lower* but *raise* the blood-pressure, at the same time that they quicken the pulse; consequently the quickening cannot be due to indirect stimulation of the sympathetic. Other drugs, however, such as nitrite of amyl, even in small doses, lower the blood-pressure at the same time that they quicken the pulse; and in their case we must raise the blood-pressure artificially.

MODE OF RAISING BLOOD-PRESSURE.—This may be done either by injecting a sufficient quantity of the defibrinated blood of another animal of the same species, warmed to 98 deg. Fahr., into the carotid or crural artery towards the heart, or by compressing the aorta. The aorta may be either compressed by the thumb of the operator, or by a narrow pad of cork laid over it and pressed upon it by a tourniquet, of which the strap has been passed round the animal's body.

MODE OF COUNTING THE BEATS OF THE HEART.—Now, if we wish to determine the blood-pressure at the same time with the pulse-rate, we may count the latter from the oscillations which each beat of the heart produces in the tracing of the kymographion, or from the sphygmoscope attached to it; but this is not always necessary, and we may wish to ascertain the pulse-rate without going to the trouble of opening an artery and using a manometer. We may do this in three ways—1. By feeling the pulse in one of the large arteries, such as the crural, with the finger; 2. By listening to the beats of the heart with a stethoscope; 3. By the motion of a needle stuck into the ventricles. For this purpose a fine harelip-needle is inserted at the point where the apex beats, and is pushed upwards into the substance of the ventricle. At its upper end it may have either a knob, or a loop to which a thread can be attached, and a barb at the point will prevent it from changing its position in the heart when traction is made upon it. In rabbits, the point where the needle should be inserted is in about half an inch to the left of the sternum in the third intercostal space, and the length of the needle used should be about three inches. Various means have been proposed for counting the oscillations more readily than can be done by simply watching the movements of the needle itself. (62) The knob of the needle may be allowed to strike against a wineglass, and the pulsations may thus be counted by the ear; or a needle without a knob may be used, and a rice-straw with a piece of bright-coloured paper attached to it may be slipped over it, so that its vibrations, amplified by the long straw, and made more visible by the bright-coloured paper, may be readily counted by the eye.

A convenient way of registering the oscillations on an upright cylinder is one devised by Professor Stricker. One of Marey's cardiographic levers is fixed on a rod close to the side of the animal and some distance above it, and a small piece of cork attached to the lever. One end of a fine thread is then fastened to the needle, and its other end pulled through a slit in the cork till it is sufficiently tight to make the lever vibrate with each movement of the needle; it is then fastened by twisting it round the lever, or by a little sealing-wax. If the lever be not raised several inches above the needle, it is pulled too much to a side and not sufficiently downwards to give a good tracing. The tracing may be taken either on plain paper with a glass-pen or camel's hair-brush attached to the lever by a piece of cork, or with a dry point on smoked paper. Instead of a vertical cylinder a horizontal one may be used, and is perhaps still better. In this case the lever should be nearly on a level with the needle, and not raised much above it.

IS THE QUICKENING OF THE PULSE DUE TO DIRECT STIMULATION OF THE SYMPATHETIC?—If so, the injection of the drug should cause an increase in the pulse-rate after the vagi have been divided as well as when they are intact. We, therefore, divide the vagi, inject the drug into the veins, and see whether or not the pulse-rate is increased. On doing this with atropia it is found that the pulse becomes slower rather than quicker, showing that the drug does not stimulate the quickening nerves of the heart. The increased rapidity of the pulse which it produces when the vagi are intact is, therefore, not due to this cause.

IS THE QUICKENING DUE TO STIMULATION OF THE CARDIAC GANGLIA?—The experiment just mentioned shows that it is not, for if it were, injection of atropia should cause quickening after division of the vagi. Supposing, however, that it had caused quickening, the question whether the acceleration was due to the ganglia or the sympathetic would have to be decided by dividing all the nerves going to the heart with a platinum-wire heated by electricity, (63) and then injecting the drug, or by applying it to the heart of the frog in a way which I shall afterwards describe. If it quickened the beats of a heart thus separated from all other nerves, it could only do so by acting on the cardiac ganglia themselves.

IS THE QUICKENING DUE TO PARALYSIS OF THE VAGI?—The exclusion of the other causes leads us to believe that it is due to this; but, in order to avoid the possibility of error, we must try to confirm our conclusion by other experiments; and, moreover, we have still to find out which part of the vagus is affected—its roots, its fibres, or its ends in the heart.

ARE THE VAGUS-ROOTS PARALYSED BY THE DRUG?—We are enabled to answer this question by our knowledge of the fact, that poisons only act on the parts to which they are carried by the blood, and that when introduced into the circulation they do not reach every part of the body at once, but are carried on with the blood-stream first to one part and then to another, and will reach a part near the point where they were introduced before one which is farther off. Thus if we inject a drug into the carotid it will be carried direct to the head, and will act on the medulla oblongata and the roots of the vagus before it reaches the heart; but if we inject it into the jugular vein it will reach the heart and act on the vagus-ends in it before it reaches the roots in the medulla. If atropia paralyse the vagus-roots, then its injection into the carotid towards the head should be followed by rapidity of the pulse more quickly than its injection into the jugular; but if it act on the vagus-ends in the heart, the pulse should become rapid more quickly after injection into the jugular vein towards the heart than after injection into the carotid. On testing this experimentally, it is found that, when atropia is injected into the jugular vein towards the heart, the pulse at once becomes quick, even before the injection is finished; but, when it is injected into the carotid towards the head, the pulse is not quickened for a quarter of a minute or more, or, in other words, till the poison has had time to pass through the capillaries of the head and go through the veins to the heart. This, then, shows that it is the vagus-ends in the heart, and not the roots in the medulla, that are paralysed by it.

ARE THE VAGUS-FIBRES PARALYSED?—From the rapidity with which paralysis of the vagus occurs after atropia reaches its ends, we have already come to the conclusion that the ends are the part affected rather than the roots or fibres; but it is well to substantiate our conclusion by further experiment. We divide the vagus and galvanise its peripheral extremity. If we do this to a normal vagus, the heart will beat more slowly or stand still altogether; but if either the fibres or ends of the nerve have been paralysed, no change will be produced in the heart's rhythm by the application of galvanism to its trunk, and this we find to be the case after the administration of atropia. But this experiment does not enable us to decide which part of the nerve is paralysed—the fibres or the ends, for in either case the effect would be the same. We may do this, however, by observing the effect which irritation of the vagus-trunk produces on such of its fibres as do not go to the heart. If it were the fibres which were paralysed, we should expect that those which go to the heart would not be the only ones affected, but that those going to other parts would be paralysed likewise.

I have hitherto spoken of the vagus as if it were a simple nerve containing only inhibitory fibres for the heart, but it is really a most complicated bundle, containing centripetal fibres having probably no fewer than eleven different functions, and centrifugal ones having nine or ten ;(64) so it is little wonder that it has long been a puzzle to physiologists, and even yet its functions are not completely investigated. Among these fibres are some which produce contraction of the œsophagus and muscles of the larynx ; and if we find that irritation of the vagus continues to produce contractions in these parts after it has ceased to render the heart's action slow, as is the case after injection of atropia, we conclude that its fibres are not paralysed. Dr. Rutherford has shown(65) that the best mode of observing the effects of irritation of the vagus on the muscles of the larynx, is to open it in front and place the animal in such a position that the light may be reflected from the inner surface of the arytenoid cartilage, as the slightest movements can then be readily detected. In this way it is found that atropia produces complete paralysis of the cardiac branches of the vagus, while the motor fibres supplying the muscles of the larynx remain unaffected ; and we are therefore forced to conclude that it acts not on the fibres but on the ends in the heart. A more direct method is to apply the drug dissolved in an indifferent fluid, such as half per cent. solution of chloride of sodium, to the vagus itself, and then to irritate the nerve above this point. This may be done by dropping the solution on the nerve after placing a piece of gutta-percha tissue below it, so as to keep the fluid from reaching the tissue below and being absorbed. If the drug paralyse the fibres the irritation which is applied to the nerve above the part which is moistened by the solution will not be conveyed by the paralysed part of the nerve, and will consequently have no effect on the heart.

HOW DOES A DRUG RENDER THE HEART'S ACTION SLOW?—We have now gone over the experiments which are necessary to determine what the structure is through which a drug quickens the heart's action, and we have now to consider those which we require when investigating the action of a drug which renders it slow. It may do so by irritating the vagus-roots, fibres, or ends ; by increasing their excitability, so that they act more strongly when stimulated ; or by paralysing the sympathetic, the cardiac ganglia, or the muscular substance of the heart itself.

DOES IT ACT BY IRRITATING THE VAGUS-ROOTS?—In order to answer this question, we divide both vagi and then inject the drug. We thus separate the heart from the vagus-roots and deprive them of any influence over it, so that, if they have been the cause of slowness of the pulse in previous experiments, it will not occur in this; but if the slowness have been due to other causes it will, with one or perhaps two exceptions, be noticed in this experiment just as it would had the vagi been intact. These exceptions, which we will consider afterwards, are increased excitability of the vagus-fibres and ends. The vagus-roots can only act on the heart through the medium of the fibres and ends; if the drug itself should affect these structures, its action on the heart may be much altered or even destroyed. If the vagus-ends be paralysed, the roots can exert no more action on the heart than they can after we have cut through the trunks; and if the excitability of the ends be increased, the power of the roots over the heart will be greatly augmented, so that the heart's action may be made slow without there being any actual irritation either of the roots or ends. In order, then, to find out what effect the drug has on the vagus-roots themselves, we must inject it into the carotid, so that it may reach them before it reaches the fibres or ends; and note what change occurs in the pulsations of the heart immediately after the injection. Any change which occurs immediately is due to the effect of the drug on the roots themselves; and, by comparing the number of pulsations at this time with that which is found a quarter of a minute or so afterwards, when the drug has reached the vagus-ends, we may discover whether their excitability has been increased or diminished. Thus, in the experiment already mentioned for ascertaining whether or not the vagus-roots are paralysed by atropia, we find that, when we inject it into the carotid, we get immediate slowness of the pulse, showing that the vagus-roots are irritated by the drug; but whenever it gets round to the heart it paralyses the vagus-ends, and the slowness at once disappears. If we were to keep the head alive by supplying it with an artificial stream of blood containing atropia, and prevent any of the poisoned blood from reaching the heart, the slowness might be continued indefinitely.

MODE OF SUPPLYING THE HEAD AND BODY WITH DIFFERENT KINDS OF BLOOD.—In his researches on respiration,(66) Hering employed a method of this sort, at one time supplying the brain with blood loaded with carbonic acid while the blood of the body was richly arterialised, and at another sending arterial blood to the brain while respiration was stopped and the blood circulating in the body was intensely venous. For this purpose he opened the thorax and tied the left carotid and innominate close to the aorta, and the vena cava superior close to the heart in a cat; he then introduced one cannula into the innominate artery, and another into the vena cava, and injected dog's blood, defibrinated and warmed, into the innominate artery, while he allowed it to flow out by the vein.

In atropia, we have an example of a drug which acts on more than one part at once, and whose action on one part completely neutralises the effect which its action on the other would produce. In the case of others, however, we have the action on the different parts strengthening each other, as in veratria, which, like atropia, stimulates the vagus-roots,(67) but, instead of paralysing the ends, increases their sensibility, and thus greatly augments the effect which the excited roots would have exercised over the heart, even had the ends remained unaltered.

ARE THE VAGUS-ROOTS IRRITATED DIRECTLY BY THE DRUG OR INDIRECTLY THROUGH INCREASED BLOOD-PRESSURE?—Along with the slow pulse, produced by the injection of atropia into the carotid, a rise occurs in the blood-pressure; and how are we to determine whether the irritation of the vagus-roots is due to this increase, or to the direct action of the drug itself? This is a question very difficult to solve in the case of atropia, on account of the rapidity with which the vagus-ends are paralysed and all influence of the root over the heart destroyed. In the case of other drugs, however, where time is allowed, the question might be settled by diminishing the blood-pressure and seeing whether or not the slow pulse returned to its normal rate, and then raising it again and observing whether the pulse again became slow.

MODE OF LOWERING AND RAISING THE BLOOD-PRESSURE.—The blood-pressure may be lowered by opening a large artery, such as the carotid or crural, and allowing the blood to flow out into a vessel warmed to 98 deg. Fahrenheit, and again raised by injecting the warm blood back into the artery. Or we may adopt Ludwig and Asp's plan,(68) of inserting into the central end of the carotid a straight tube with a stopcock in its middle, and the moist bladder of a small animal, well emptied of air, tied to its free end. When the stopcock is opened, the blood rushes from the carotid into the bladder, and the tension in the arteries is diminished; but, when we press the blood out of the bladder back into the arteries, the tension on them is again increased.

ARE THE VAGUS-ROOTS IRRITATED REFLEXLY FROM SOME OTHER PART OF THE NERVOUS SYSTEM?—There are two ways of deciding this: the first is to inject the poison in such a manner that it shall reach the vagus-roots before it reaches the other nervous structures through which we suspect it to act reflexly; the second is to remove these nervous structures themselves, or to destroy their function by means of some other poison. Thus, if we think that atropia, when injected into the carotid, acts on the medulla through the cerebrum, we may either remove the latter, or abolish its function by opium or chloral. The application of irritating vapours, such as ammonia or tobacco-smoke, to the nasal mucous membrane of a rabbit, produces still-stand of the heart. We ascertain that this is due to irritation of the vagus by cutting it and finding that the vapour then has no effect; and we next decide that the irritation is conducted to the nervous centres through the trigeminus and not through the olfactory nerve, by observing that section of the former likewise prevents the action of the vapour on the heart, while section of the latter does not affect it. (69)

ARE THE VAGUS-ROOTS IRRITATED INDIRECTLY BY THE DRUG IMPAIRING RESPIRATION, AND THUS ALLOWING CARBONIC ACID TO ACCUMULATE IN THE BLOOD?—In the experiment just mentioned, we have ascertained that the vagus is irritated, and that irritation is conducted to the nerve-centres through the trigeminus, but we do not know that the irritation is directly reflected from the trigeminus to the vagus. It might be due to irritation of the vagus-roots by carbonic acid, which has accumulated in the blood from impeded respiration; for the irritating vapour applied to its nose causes the rabbit to close its nostrils and stop breathing for a while if the trigeminus be intact, but when it is cut no irritating impression can be conveyed to the brain, and so no closure of the nostrils takes place, either voluntarily or reflexly. The rabbit, therefore, continues to breathe freely; no carbonic acid accumulates in the blood, and no irritation of the vagus occurs. Other drugs, such as strychnia and curare, etc., impede respiration—not by causing closure of the nostrils and consequent obstruction to the passage of air to the lungs, but by acting on the muscles and nerves and diminishing the respiratory movements. Strychnia does this by producing tetanic contraction of the respiratory muscles, curare by paralysing them, and chloral by diminishing the excitability of the respiratory nervous centre. In all such cases, in order to ascertain that indirect irritation of the vagus from impeded respiration is not the cause of the slowing of the pulse, we insert a cannula into the trachea and begin artificial respiration; we then note the rate of the pulse and blow the irritating vapour into the nostrils, or inject the drug into the veins, and see whether or not the pulse is rendered slow, taking care to keep up artificial respiration all the time. If the drug cause convulsive movements which interfere with the proper performance of artificial respiration, curare should be given so as to prevent their occurrence, and the experiment should be again repeated.

ARE THE VAGUS-FIBRES IRRITATED?—To ascertain this we apply the drug dissolved in an indifferent fluid, such as a solution of half per cent. of chloride of sodium, or serum, to the nerve, and notice whether any change occur in the heart-beats. Care must be taken that the solution of the drug be not applied in too concentrated a solution, as it might then have an irritant action, which it could not have if it reached the part through the circulation and became diluted by the blood before reaching the nerve, and false conclusions might thus be arrived at.

IS THEIR CONDUCTING POWER INCREASED, SO THAT THE ROOTS CAN ACT THROUGH THEM ON THE HEART MORE READILY AND POWERFULLY?—If their conducting power be increased, other stimuli as well as those from the roots will act more powerfully on the heart. We therefore divide the vagi and apply a stimulus to the peripheral end of one or both by irritating them with one of Du Bosi Reymond's induction-coils, and note at what distance from the primary coil the secondary one must stand in order to produce stoppage or slowness of the heart; we then apply the drug to the nerve below it and again irritate. If the excitability of the nerve be increased, stoppage or slowness should be produced when the distance between the primary and secondary coils is greater—that is, when the current is weaker than before. It is generally assumed that the fibres are not likely to be affected, and these experiments are rarely performed.

ARE THE VAGUS-ENDS EXCITED?—We may test this in the same way as the action on the roots, by injecting the drug at one time into the jugular and at another into the carotid. If it increase the excitability of the ends without affecting the roots, we should find it produce, when injected into the jugular vein, an immediate slowing of the pulse, which does not become greater in a quarter of a minute afterwards, when the drug has reached the roots. When injected into the carotid, no slowness should occur till sufficient time has elapsed for it to pass round to the heart. If it increase the excitability of both roots and ends, immediate slowness should occur, whether it be injected into the jugular or carotid, and this should become more marked after fifteen or twenty seconds. If, like physostigma, it increase not only the excitability of the vagus-ends, but that of the quickening centre in the head, injection into the jugular should be followed by immediate slowing, which would become less marked when the drug reached the head, and injection into the carotid by an immediate quickening, which would become less or give place to slowness when the drug reached the heart.

At first sight one might think that, after time had been allowed for the drug to pass round the circulation and be applied both to the vagus-roots and ends, its action on the heart would be the same whether it had been originally injected into the jugular or into the carotid ; but this is not the case, for that organ towards which the drug was injected gets a larger dose, and its action is more strongly excited than that of the other. Thus when physostigma is injected into the carotid, the quickening centres are stimulated and the pulse-rate rises ; and, although the pulse falls somewhat after the vagus-ends have also been acted on, it nevertheless continues above the normal, the stimulation of the vagus-ends not being able to counteract the still more excited quickening centres. When it is injected into the jugular, the vagus-ends get the largest dose ; and, although the pulse, which is at first made very slow, may afterwards become quicker when the drug reaches the brain ; it nevertheless does not reach the normal rate, the quickening centres being unable to counteract the more strongly excited vagus. I the vagus be then cut, however, the pulse becomes quicker than it would have done had no physostigma been given; or, if the vagi be first cut and the drug injected, the pulse is quickened at once.(70) One might think that, since the drug acts on the vagus-ends, its action should remain after the nerves themselves have been divided ; but since it is by increasing the excitability of the ends that it acts, if we separate these ends from the roots, and thus remove their normal stimulus, their increased excitability can have but little effect. In order to measure the amount of increase in the excitability of the nerves, we divide the vagi and irritate them by an induction-coil, noting the strength of current required to produce still-stand or slowness of the heart before and after injection of the drug into the veins.

IS THE SYMPATHETIC PARALYSED?—This is tested by cutting the vagi and dividing the spinal cord between the first and second cervical vertebræ, so as to exclude the action of those centres in the head which quicken the heart and raise the blood-pressure ; the drug is then injected, and the sympathetic irritated by an induced current and the pulse counted. If it be quickened by the irritation, the sympathetic is not paralysed.

ARE THE CARDIAC GANGLIA PARALYSED?—To see whether or not the nervous structures contained in the heart itself are acted on by a drug, we must separate it from all other nerves passing to it from without, and prevent its being acted on by anything other than the drug, such as altered blood-pressure or temperature. This is done in mammals by dividing the vagi, the sympathetic cord, the depressor, and the spinal cord between the first and second cervical vertebræ. The heart is thus separated from the quickening and retarding centres, so that any alteration in its beats must be due to the nerves contained in its walls, or the muscular fibre of these walls themselves; at the same time the vessels are separated from the vaso-motor centre, and the heart is thus protected from the effects of any change in the blood-pressure, except the generally unimportant ones produced by the action of the drug on the vascular walls. The number and amplitude of the heart's contractions are then registered by a needle placed in the ventricle, and the blood-pressure by the manometer; poison is injected into the jugular, and the tracings taken afterwards are compared with those taken before. If we find that the heart-beats have become slower and weaker, while the pressure they have to overcome has not been increased, we may conclude that the motor nerves or the muscular substance of the heart have become paralysed. If the blood-pressure have risen, blood should be allowed to flow from an artery till it falls to its previous level, and then tracings should be taken with the needle for comparison with the previous ones.

The action of drugs on the heart can be studied still better in the frog than in mammals, as the heart of the former can be completely separated from the body, so that the drug can be applied to it alone. After its removal it continues to pulsate just as before, and, consequently, any action of the drug on the rhythm or force of its beats can be very easily noticed. The usual way of making experiments on this subject formerly was to take out the heart and lay it in a solution of the poison, or, what was better, to take two glasses containing solution of chloride of sodium (half per cent.) and add a little of the drug to one of them. A frog's heart was then laid in each, and the beats of the poisoned compared with those of the unpoisoned one. Both of these plans are inferior to that of Ludwig, who supplies the heart with serum so as to keep it as nearly as possible in a normal condition, and attaches to it a manometer, so that it may itself register the number and form of its beats, and give more exact indications than could be obtained by merely looking at it. The apparatus which he and Cyon first used, and which is figured in his *Arbeiten* for 1866, has been considerably modified by Dr. H. P. Bowditch, and is shown in fig. 10. It consists of a bent glass tube (C C′ C″), which is supported by a glass plate (D). The frog's heart (A) is connected to the ends of this tube by means of India-rubber tubing and two glass cannulæ, one of which (B) is tied into the vena cava and the other (B′) into the aortic bulb. The tube has three openings, each of which is furnished with a three-way glass stopcock. By means of one of these (C) it can be filled with serum

Fig. 10.

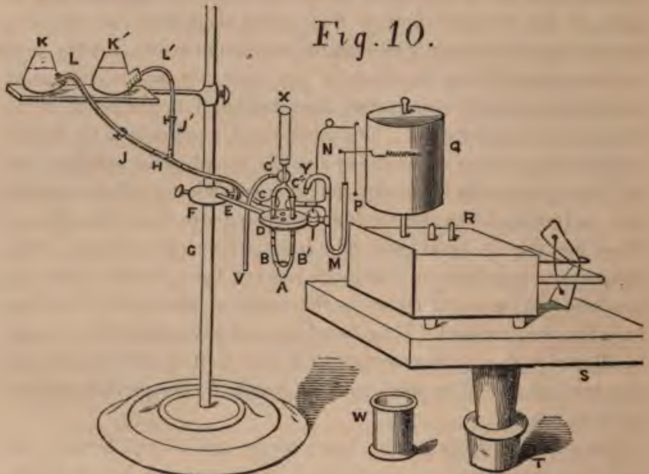


Fig. 10.—Dr. H. P. Bowditch's apparatus for experiments on the heart of the frog. A is the frog's heart. B is a cannula tied into the vena cava, and B′ one into the aortic bulb. C, C′, and C″ are three glass stopcocks. By C fresh serum is supplied, by C′ old serum is let out, and C″ allows the communication between the bent tube B C′ B′ and the manometer M to be opened or shut at will. D is a glass plate through which the bent tube B C′ B′ passes. E is a rod ending in a ring into which D is fitted. F is a nut by which the whole apparatus can be moved up and down on the stand G. H is a T-tube. J and J″ are two clips to stop the flow of serum from K or K′. K and K′ are two fountain-bottles for supplying serum to the heart. K contains pure, and K′ poisoned serum. L and L′ are bent tubes which convey the serum out of K and K′. M is a small manometer. N is the pen or point which swims on the mercury. The horizontal part is made of glass; the vertical rod of esparto grass, with a small piece of sealing-wax at its lower end. The tracing may be made with ink, or with a dry point on smoked paper. P is a small weight which hangs by a piece of unspun silk from a bent wire, and keeps the pen resting on the paper. Q is the revolving cylinder. R is the clockwork, which is provided with one of Foucault's regulators. S is a table, which can be raised or lowered at pleasure, and fixed at any height by the screw T. V is an India-rubber tube through which the serum is emptied from X. X is a graduated tube into which the serum is allowed to pass after it has circulated some time. Y is an India-rubber tube, which is generally closed by a clip, but is opened when the apparatus is to be filled, or when we wish to let down the mercury to zero, in order to draw an abscissa. W is a glass vessel, which fits tightly to the under side of D, and protects the heart from external irritation. Into the two holes seen in D, tubes may be fitted air-tight, and the heart made to pulsate in an atmosphere of any sort of gas.*

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* This apparatus is made by Geisler, Blume's Hof, Berlin. Mr. Hawksley, of Blenheim Street, Oxford Street, has adapted a bobbin and rollers to the revolving cylinder figured above, so that it will carry a continuous roll of paper, and may be conveniently used instead of the kymographion shown in Fig. 7. The instruments which I have already described as necessary for experiments, may be obtained from him or from Oswald Hornn, Schiller Strasse, Leipzig.

from a reservoir (K or K′), and the stopcock may be so turned as to allow serum to enter the part of the tube above it, the part below it, or both together, or the communication with K may be shut off while the lumen of the tube remains open. By C′, the serum which has been already used is allowed to escape, when a fresh supply is given, and C″ allows the tube to communicate with a manometer (M), on the mercury in which a fine pen floats and registers its oscillations on a revolving cylinder (Q). Each time the heart contracts, it drives the serum with which it is filled out of the ventricle, round the tube, and back through the vena cava into the auricle, and at the same time raises the mercurial column in M. The height of the curve traced by the pen depends very much on the amount of serum which the heart contains, being very much higher when the heart is full; and it must, therefore, be equally filled each time, or very different tracings will be obtained. For this purpose I use, as reservoirs for the serum, fountain-bottles, in the mouth of which it always stands at the same level, and, consequently, always fills the heart at the same pressure. One of them (K) is filled with pure serum, and the other (K′) with serum to which a certain amount of the drug to be tested has been added.

For the purpose of introducing the cannula into the heart, the brain and cord of the frog are destroyed by a piece of wire, and the animal fixed on its back to a board. A V-shaped incision, with its apex at the lower end of the sternum, and its limbs extending upwards and outwards towards the fore-arms, is then made in the skin, and the flap turned back or cut off. The sternum is then removed in a similar way. The pericardium is next opened, the cut being made while the heart is contracted, so as to avoid injuring it. The apex of the heart itself is then turned upwards, and two ligatures are passed underneath a small vein which runs from its posterior surface to the pericardium. The ligatures are tied, and the vein is cut between them. The pericardium must now be removed entirely from the heart, and the vena cava superior and the right branch of the aorta tied. The vena cava inferior is carefully isolated; a ligature is passed under it; a short and wide cannula tied into it, and another into the left branch of the aorta. The heart is then cut away from the body. Both cannulæ are filled with serum, and connected by India-rubber tubing to the ends of the tube C C′ C″, care being taken to exclude air-bubbles. The end of the manometer nearest C is filled with serum by opening the clip at Y, and allowing all the air and a little serum to escape. The clip is then replaced, and the heart allowed to beat once or twice, with the stopcock

C and the clip J freely open, so that it may become full of fresh serum. The stopcock C is then turned so as to cut off the tube C C' C'' from all communication with K; and tracings are then taken, an abscissa or zero-line being drawn under each. The heart is next supplied with poisoned serum from K', and the tracings which it gives are compared with the normal ones. By slightly turning the stopcock C, a greater or less resistance may be opposed to the circulation of fluid, and the effects thus imitated which contraction or relaxation of the vessels would produce in the living animal.

Another apparatus has been invented by Ludwig, and used by Coats in his research on the vagus,(71) in which there is no circulation, the serum being simply forced out of the ventricle at each systole, and falling back at each diastole. It gives, however, very good tracings of the number and form of the heart-beats, and is extremely well adapted for observations on the effects of drugs on the vagus. Its consists of a manometer, E, and a reservoir, A, with which the frog's heart is connected by two cannulæ, D and D. The frog's heart is prepared by destroying the brain and spinal cord, removing the sternum and fore legs, but leaving a large flap of skin, S, to cover the heart with, and then introducing a cannula into the vena cava and aorta, as in the former experiment. Instead of then cutting out the heart, the liver and lungs are removed, and the stomach is cut through the middle; and a glass tube, sealed at both ends, and as thick as the œsophagus will admit, is pushed through it till one end projects at the mouth and the other from the cut end of the stomach. The vagus is thus clearly displayed; and, in order to isolate it more perfectly, all other nerves should be cut away, as well as a part of the pharynx, so that no soft parts may touch it from its exit from the bone to the place where it crosses the aorta. From this point to the heart, it should be left untouched; and the jugular vein should not be tied, so as to leave it undisturbed. The glass tube, J, is then fixed firmly in a holder, L, and the cannulæ, D and D', connected with the reservoir, A, and the manometer, E. Instead of the reservoir A shown in the figure, it is perhaps better to use two fountain-bottles. The apparatus is used just like that shown in Fig. 10; and the heart should in this case also be filled so full that a certain tension exists within it even during diastole. The amount of this is shown by the height of the diastolic curve above the zero-line. When the vagus is irritated, the tension during the diastole sinks; but, if its inhibitory fibres be paralysed by atropia, which leaves its quickening ones unhurt, irritation has then the opposite effect, and

Fig, 11.

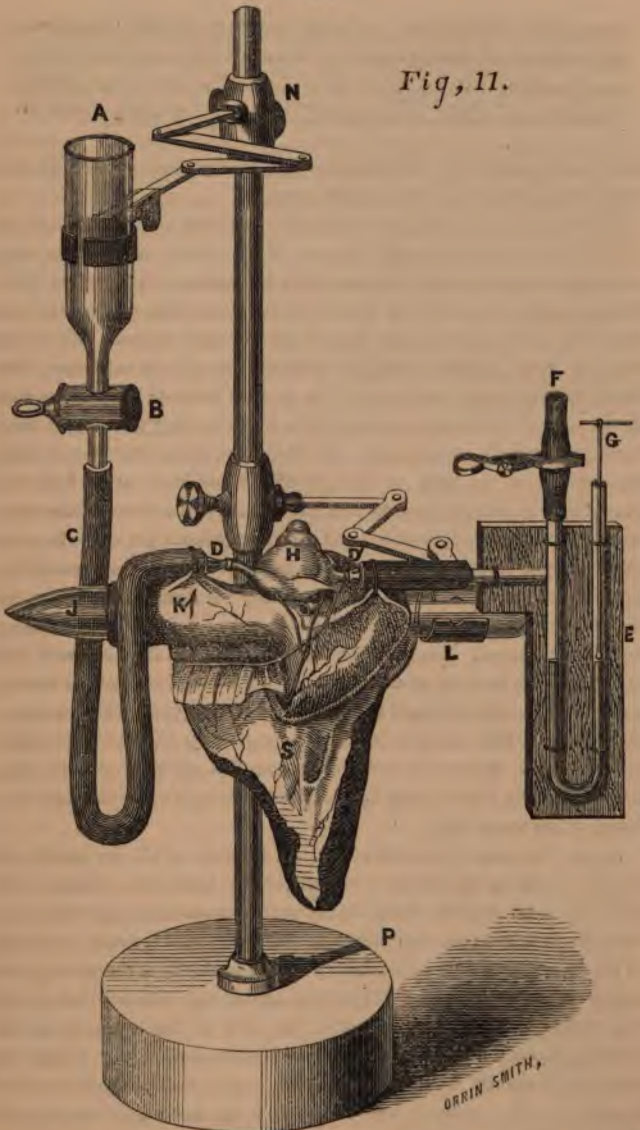


Fig. 11.—Ludwig and Coats' frog-heart apparatus. A is a reservoir for serum. B. A stopcock to regulate the supply to the heart. C. A piece of caoutchouc

tubing connecting A and D. D. A glass cannula in the vena cava inferior. D′. Another in the aorta. E. A manometer. F. A piece of tubing closed by a clip, to allow of the escape of serum. G. A fine pen, floating on the mercury in E. H. The frog's heart. J. A sealed glass tube passed through the œsophagus K, and firmly held by a holder L. M. A nut which allows L to be moved up and down. N. A second holder to support A. P. A stand with upright rod. Q. A flap of skin to cover the heart and prevent drying. V. The vagus.

the tension during the diastole becomes greater and greater till the heart may stand still in firm contraction.(72)

WHAT PART OF THE GANGLIONIC APPARATUS IN THE HEART IS AFFECTED ?—In dealing with this part of the subject, we tread on very unstable ground, for here pharmacology has almost run ahead of physiology; and even with our physiological knowledge of the nervous structures of the heart a great deal of speculation is mixed. We know that the heart contains ganglia scattered through its substance, but found in the greatest numbers in the septum between the auricles and in the auriculo-ventricular groove of the frog's heart,(73) in which they have been chiefly investigated. As the heart, long after it has been separated from the body, or the apex after it has been cut off from the ventricle, will still continue to beat rhythmically, the cause of the contractions must be contained in itself; and we assume the cause in each part to be the cardiac ganglia, and suppose that they are connected by some apparatus which keeps them working harmoniously together, as the different parts of the heart all contract in a definite order so long as it is uninjured. Their action may be rendered slow or quick by nerves passing to them from without, both the retarding and the quickening nerves being contained in the vagus in the frog(74); while in mammals the retarding ones are found in the vagus,(75) and the quickening ones chiefly in the third branch of the ganglion stellatum(76) (or first dorsal generally joined to the last cervical), although some may also be found in the vagus.(77)

Some physiologists consider that the function of all the ganglia is simply to keep up rhythmical movements in the heart.(78) Others hold that only some of them, found chiefly in the venous sinus and ventricle, have this function(79); while others are inhibitory, and restrain the action of the former.(80) These inhibitory ones exist chiefly in the septum between the two auricles.(81) The reason of this supposition is that, when the venous sinus is separated from the rest of the heart, it continues to pulsate; but the auricles and ventricles stand still. When the ventricle is cut off from the auricles, it begins to beat again, but the auricles do not; so that it would seem as if the motor apparatus in the venous sinus and ventricles together could overcome the inhibitory apparatus in the auricles, and keep the heart going; but that this is too strong for the motor ganglia in the ventricle alone, and will not let them go on till they are separated from it, or till it becomes exhausted, which it seems to do after a little, and then both auricles and ventricles begin anew. The physiologists who hold the simpler view, say that this stoppage is only due to the irritation of the vagus-fibres which run along the venous sinus, and that the renewed cardiac contractions are simply due to the irritation passing off. (82) The pharmacologist, however, is not contented even with the more complicated of these mechanisms, but demands a still more elaborate nervous apparatus in order to explain the action of poisons on the heart. (83) The necessity for this has been clearly shown, and a plan of the nerves drawn up, by Professor Schmiedeberg. I have endeavoured to represent the supposed nature of this apparatus in the accompanying diagram. It consists of a ganglion, M, which keeps up a rhythmical contraction of those muscular fibres of the heart to which it is connected by the fine nervous filaments, E. This ganglion is connected by an intermediate apparatus with an inhibitory ganglion, I, which can retard or stop the muscular contractions which M produces; and by another apparatus, C, with another ganglion, Q, which quickens the contractions. I is connected by an intermediate apparatus, A, with the retarding fibres, V, of the vagus, and D with the quickening nerves, S, of the heart.

Fig: 12

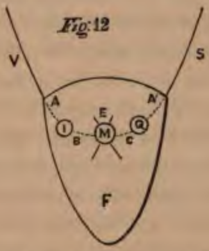


Fig. 12.—Diagram of the hypothetical nervous apparatus in the heart. M. Motor ganglion. I. Inhibitory ganglion. Q. Quickening ganglia. V. Inhibitory fibres; and S, quickening fibres from the head. A, A', B, and C, intermediate apparatus. E. Fibres passing from the motor ganglia E, to the mnscular substance F. For simplicity's sake, only one set of motor ganglia has been represented, but other similar ones are to be supposed to be present in other parts of the heart, and so connected with this set that they all work in unison. It must be remembered that this diagram is purely hypothetical: but if this be carefully borne in mind, the sketch will be found of service in remembering and comparing the action of different poisons on the heart.

INHIBITORY GANGLIA OF HEART.—We have hitherto included under the terms vagus-ends all the inhibitory apparatus in the heart;

but, when we begin to experiment with the heart alone, we find that poisons which such experiments as have already been described would lead us to class together, as acting on the vagus-ends, really act on very different parts of the cardiac nervous system. Thus nicotia, when injected into the blood after the vagi and cord have been divided, renders the pulse slow; but this soon gives way to quickening; or, if the dose be large, quickening may occur at once; and, if we then irritate the vagus, we find that we cannot render the heart beats slow any more than we can after poisoning by atropia. (84) We thus see that, after the irritation which nicotia first occasions in the vagus-ends has passed off, it paralyses them; and we might thus be inclined to think that they acted on the same structures. But, if we give nicotia to a frog, and instead of irritating the vagus, we irritate the venous sinus, still-stand of the heart is at once produced; while, if atropia be given, and the venous sinus then be irritated, the pulsations are not slowed at all —showing us that there is some inhibitory apparatus in the venous sinus which has been paralysed by atropia, but left untouched by nicotia. We may substantiate this conclusion by another and extremely useful method of investigation—viz., by administering another poison, and seeing how its action is affected by each of the other two. If we allow a little muscaria to reach a frog's heart, its beats become slower and slower, and at last cease altogether; the ventricles remaining widely distended, just as they would do if the vagus were strongly galvanised. If nicotia be then injected into the frog or mixed with the serum supplying an excised heart, no alteration is observed; and, if nicotia be injected before the muscaria, the latter poison stops the heart just as usual, although the nicotia may have so paralysed the vagus that no irritation whatever applied to its trunk could act on the heart. But, if atropia be used instead of nicotia, the effect of the muscaria is at once destroyed, and the heart, which was standing quite still, immediately begins to beat. (85) If the atropia be applied first, and muscaria given afterwards, it has no effect. Hence we see that nicotia has paralysed some part of the inhibitory apparatus farther away from the motor ganglia than that on which muscaria acts, while atropia has acted either on the same part as muscaria, or on some other one which lies between it and the motor ganglia.

Now, as the inhibitory effect produced by muscaria is not developed all at once, but goes on slowly increasing till it makes the heart stand still in diastole, it seems probable that its stimulating action is exerted on a ganglion, rather than on a nerve-fibre; and we therefore suppose that it acts on the inhibitory ganglion I. (86) As the action of nicotia is exerted on something farther from the heart than I, our first idea is, that it must be the nerve-fibres V. But, on applying nicotia to the trunk of the vagus, after fixing the heart in Coats' apparatus, we find, on irritating the nerve above the point, that it still conducts impressions and causes stoppage of the heart. We are thus led to suppose the existence of an intermediate apparatus on which nicotia acts; but, whether or not this intermediate part simply consist of nerve-fibres less protected from the poison than those in the trunk, we cannot say. As atropia destroys the action of muscaria, it may act like muscaria on I; but the fact that muscaria does not destroy that of atropia would lead me to refer the action of the latter to a part between I and M, which is represented by B. Of what nature this part is, we know nothing; but that such a part exists, is rendered all the more probable by the mutual antagonism of atropia and physostigma. Although this latter poison renders the vagus very sensitive, so that the power of any irritation applied to its trunk to stop the heart is immensely increased,(87) yet it has not the extraordinary power of producing stillstand of the heart possessed by muscaria. Unlike muscaria, however, it has the power of removing the paralysis of the vagus produced by atropia; and, though an additional dose of atropia will again cause paralysis, a second dose of physostigma will again remove it.(88) This difference of action between muscaria and physostigma seems to show that they act on different nervous structures; while the mutual power that atropia and physostigma possess to neutralise each other's effects, indicates that atropia acts on the same structure as physostigma, and consequently on a different one from muscaria.

ANTAGONISM OF ATROPIA AND PHYSOSTIGMA.—Atropia and physostigma are thus physiological antidotes to each other; and Fraser has shown that a dose of physostigma large enough to kill an animal may be given to it with impunity, if atropia be administered along with it; and that the animal may be afterwards destroyed by a small dose given alone.(89) It is true, they do not completely counteract each other's action, each one seeming to produce several effects, some of which, and these the most deadly, are neutralised by those of the other drug, while others are not so neutralised; and, if enormous doses be administered, those active effects which are not neutralised may become so powerful as to cause death, although they are comparatively unimportant when the dose is small.(90)

IMPORTANCE OF THIS IN THERAPEUTICS.—Nevertheless, within certain limits these poisons do antagonise each other most successfully;

and this observation seems to me to have a most important bearing on the treatment of such diseases as have their origin in morbid matter introduced into the system, for it shows that it is not always necessary to eliminate a poison in order to remove its effects, but that it may be neutralised and rendered innocuous while still present in the organism; and seems to indicate that, for the treatment of zymotic diseases, we should seek to discover such remedies as will counteract the effects of the poisons on which they depend, and not merely endeavour to quicken their elimination.

ACTION OF VARIOUS DRUGS ON THE INHIBITORY APPARATUS.—From experiments which he has made on the excised hearts of frogs with Ludwig and Coats' apparatus, Boehm(91) has come to the conclusion that conia paralyses the terminal filaments of the vagus; nicotia the intermediate structure between them and the inhibitory ganglia; and that others, such as atropia, hyoscyamia, daturia, physostigmia, aconitia, delphinia, and veratria, diminish or destroy the irritability of the inhibitory ganglia themselves. It is rather extraordinary to find physostigmia in this list; and it would thus seem that the pure alkaloid which Boehm used had a different action from the tincture used by Von Bezold, unless it be that the result depends simply on a difference in the amount of the poison used.

ACCELERATING GANGLIA IN THE HEART.—We infer the presence of quickening ganglia in the heart, from the effects produced by irritating the vagus after its inhibitory power has been destroyed by the administration of nicotia or atropia. When irritation is then applied to the nerve, it no longer produces retardation, but, on the contrary, a decided acceleration of the cardiac pulsations. This shows that the vagus contains fibres which quicken the heart, and that these are unaffected by the drugs which have paralysed the others. The quickening, however, does not take place till some time after the application of the irritant; and, if it be applied only for a short time, no acceleration may take place till after its removal; but, after it does occur, it remains for a considerable time. If we irritate the heart directly, instead of irritating the nerve, its beats are quickened at once, and the acceleration does not last long after the irritation is discontinued. This shows that, when we stimulate the quickening nerves, we do not act directly on the motor ganglia M (Fig. 12), as we do when we irritate the heart itself, or as we should do if the quickening fibres ended directly in them; and we therefore infer the existence of the accelerating ganglia Q between the quickening nerves S and the motor ganglia M.(92) The accelerating apparatus seems to be stimulated by veratria; for we find that the cardiac pulsations are increased by its administration to mammals in which the spinal cord, vagi, sympathetics, and depressors, have all been divided, or when it is applied to the excised heart of a frog (93.)

IS QUICKENING OF THE EXCISED HEART DUE TO PARALYSIS OF INHIBITORY OR STIMULATION OF ACCELERATING GANGLIA?—It is possible that the quickening may be due to paralysis of the inhibitory ganglia in the heart, and not to stimulation of the quickening ganglia. This can be decided by paralysing the inhibitory ganglia by means of atropia, before applying the poison to be tested—*e.g.*, veratria. If the latter poison exercise a stimulating action on the quickening ganglia, it will quicken the heart after atropia has been applied. If it simply paralyse the inhibitory ganglia, it will have no further effect after their power has been destroyed by atropia. In the diagram, I have figured intermediate structures C and D between the quickening nerves and ganglia, so as to correspond with those of the inhibitory apparatus; but whether they really exist or not, we cannot at present say.

IS THE CO-ORDINATING APPARATUS OF THE CARDIAC GANGLIA PARALYSED?—Regarding this apparatus we know almost nothing. When the heart is dying, its rhythm is often disturbed, and two or three contractions of the auricles may occur for every contraction of the ventricle. When laudanum is poured into the heart, the rhythm is quite reversed; for after each pause the ventricle contracts first, and contraction of the auricle follows it (94). Digitalis and some other poisons cause peristaltic movements in the ventricle; and occasionally some spots in the ventricle continue to pulsate while the rest of it remains firmly contracted and motionless (95). These effects are probably due to disturbance of the apparatus which connects the different motor ganglia in the heart and causes them to work in unison.

ARE THE MUSCULAR FIBRES OF THE HEART PARALYSED?—We test this by applying an irritant to them directly, and seeing whether or not they contract. If the motor ganglia be uninjured, the application of an irritant generally produces a rhythmic contraction of the whole heart; but, if they be paralysed while the muscular fibre is healthy, the irritation only causes a local contraction of the part to which it is applied.

BLOOD-PRESSURE.—The blood-pressure depends on two things—1, the activity with which the heart pumps the blood into one end of the arterial system; 2, the rate at which it flows out at the other end into the veins. The rate is regulated by the small arteries and capillaries, which dilate and contract so as to quicken or slow it. The power of contraction is denied to the capillaries by many physiologists; but Stricker has, I think, conclusively shown that they do possess it (96).

The rapidity with which the blood flows through them does not depend entirely on the width of the capillaries, but also on the pressure on the arteries which is forcing the blood into them. The higher this is, the more rapidly does the blood flow; and in proportion as it diminishes, does the current become slower. From this circumstance we can judge of the force of the heart-beats from the form of the curve which we obtain with the sphygmoscope. When the heart contracts with great force, it drives the blood out of the ventricle into the arteries so quickly that there is no time for much to escape from the capillaries while the systole lasts; and so the tension rises high. This increased tension makes the blood run quickly out of the capillaries, and we have a fall of pressure, rapid at first, but gradually becoming slower as the tension diminishes. This is shown in Fig. 13. When the heart contracts less forcibly, it sends in the blood more slowly, and there is time for a greater quantity to escape by the capillaries during the systole; and the tension does not rise so high. From the tension being lower, the outflow of blood is not so quick; and the pressure therefore sinks more gradually than in the former case. This is represented in Fig. 14. Both of these figures were obtained by connecting a sphygmoscope with a schema of the circulation such as I have already described, and compressing the India-rubber ball which represented the heart with greater or less force and suddenness; care being taken, however, to empty it completely each time, so that the amount of air sent out should always be alike.

Fig. 13.

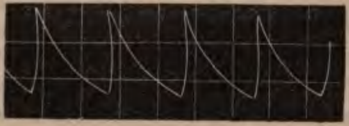
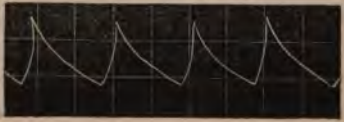


Fig. 14.



As variations in the blood-pressure may be due to alterations in the activity of the heart or the size of the capillaries, or to both together, we cannot say when it is due to the one and when to the other, unless we can keep one of them constant while we allow the other to alter, or unless we examine them both separately.

ELIMINATION OF THE ACTION OF THE HEART.—We may keep the action of the heart tolerably constant, and thus ascertain with considerable exactitude the action of any drug on the exit-tubes—whether they be arterioles or capillaries matters not—by separating the heart from the nerve-centres, and then injecting the drug into the circulation.

DIVISION OF CARDIAC NERVES.—This separation can be effected to a considerable extent by dividing the sympathetics, vagi, and depressors in the neck; but it is done much more effectually by dividing the nerves near their entrance into the heart by a fine wire heated by means of a galvanic battery (97).

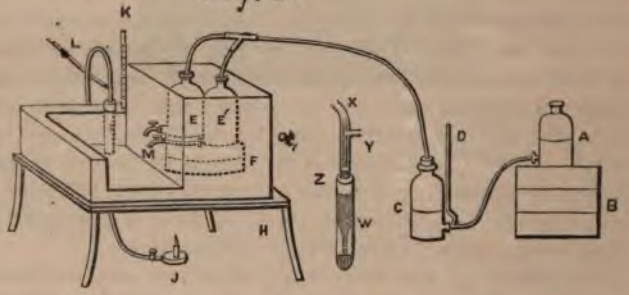
As poisons generally produce their most marked effects on the heart of mammals through the nervous centres whose connexion with the heart we have thus severed, alterations in the blood-pressure will be due to changes in the vessels, except in so far as the drug may have affected the cardiac muscle or ganglia. But, just as we obtained the most exact results when we examined the heart altogether apart from the blood-vessels, so we shall probably come to the most satisfactory conclusions regarding the vessels by observing them apart from the heart. You will remember that, during the diastole, the circulation is carried on entirely independently of the heart by the pressure of the blood in the arteries; and, if we can prolong the diastole sufficiently, we shall be able to tell whether the vessels are dilated or contracted by simply seeing whether the pressure sinks quickly or slowly.

If we prevent any blood from being pumped into the aorta by the heart, the arterial system will come to resemble a bottle with a hole in it, from which the fluid which it contains is running. The larger the hole, the more quickly will it run out and the bottle become empty, and *vice versâ;* and, in the same way, the more dilated the capillaries are, the quicker will the blood run out of them into the vein, and the pressure sink in the arteries; the more contracted the capillaries are, the more slowly will the blood flow through them, and the more gradual will be the fall of pressure. In the case of many poisons, we may do this by irritating the vagi before poisoning, and seeing how quickly the pressure falls while the heart is standing still; and then repeating the experiment after injecting the poison. If the pressure fall more quickly in the second case, we know that the vessels have become dilated; and if more slowly, that they have contracted (98). Of course, only those parts of the tracings in which the pressure has been the same are to be compared with each other; but, if we stop the heart long enough, we can always get parts in both which are capable of comparison.

When the poison paralyses the vagus, as atropia does, this method fails; and then we must open the thorax, perform artificial respiration, and put a ligature round the aorta.

ARTIFICIAL CIRCULATION IN MAMMALS.—As an animal quickly dies when the aorta is ligatured, it is better to carry on artificial circulation by a syringe through a cannula inserted into the aorta, as Hering (99) has done in his researches on the connexion between arterial movement and respiration. After the blood has circulated once, it may be defibrinated, shaken with air, warmed to 40 deg. Cent., and reinjected. Instead of using a syringe, the cannula in the aorta may be connected with the nozzle M, Fig. 6, and the blood put in the flask 3. It can thus be kept at a constant temperature more easily than when a syringe is employed. The pressure may be alternately increased and diminished so as to imitate the beats of the heart by raising and depressing the flask A. This may be done by passing a string over a pulley, and attaching one end to the flask and the other to a treadle worked by the foot. Warm blood has the disadvantage, that it undergoes change and becomes decomposed quickly; and cold blood may, therefore, be sometimes preferred. When cold blood is employed, only the flask which contains the blood is necessary; and it may be raised or lowered in the same way as the other.

Fig. 6.



ARTIFICIAL CIRCULATION IN FROGS.—Artificial circulation may be kept up in frogs by simply inserting a cannula into the aorta, and allowing blood to flow into it from a raised reservoir, as done by Rollett (100). By using two, as in the experiments on the frog's heart, normal blood may be allowed first to circulate through the vessels; and, the web being put under the microscope, their diameter may be measured; and then poisoned blood may be allowed to flow through them, and any change in their diameter noticed.

OBSERVATION OF VESSELS.—The parts best adapted for observing changes in the size of vessels in mammals are the ear in rabbits and the mesentery. When the mesentery is chosen for observation, the abdominal parietes should be divided; but the peritoneum should not be opened, as changes in the diameter of the mesenteric vessels may be observed through it, and they are thus protected from the disturbing element which the irritation produced by the access of air to them would introduce into the experiment. The vessels in the rabbit's ear are readily measured by a micrometer used with one of Brücke's magnifiers, which is simply a telescope with an extremely short focus. The ear should be held up so as to allow the light to shine directly through it, and the magnifier placed horizontally.

The area of the capillaries may be lessened, and the flow of blood through them retarded in two ways; 1, by contraction of their walls; 2, by pressure exerted on them from without. They may be made to contract by irritation, 1, of the vaso-motor centres, 2, of the vaso-motor nerves, or, 3, of their muscular walls; and pressure may be exerted from without by the motions of muscles or of organs composed of involuntary muscular fibre such as the intestines. The movements of respiration also, as already mentioned, exercise an important influence on the pressure.

ELIMINATION OF RESPIRATION AND MUSCULAR MOVEMENT.—The influence both of respiration and of muscular movement may be eliminated by giving the animal curare, and keeping up artificial respiration, before beginning to experiment with the drug whose action we wish to examine.

ELIMINATION OF VASO-MOTOR CENTRE.—For the purpose of ascertaining whether the drug has acted on the vascular walls or on the vaso-motor centre, we divide the vaso-motor nerves going to a part before injecting it, and see whether it acts as it would have done had they been undivided. Thus, when we are observing the rabbit's ear, we divide the sympathetic in the neck; and, when looking at the mesentery, we cut the splanchnics before the injection, and see whether the vessels contract or dilate as we have previously seen them do under influence of the poison in animals in whom the nerves were intact.

For the purpose of ascertaining whether the drug acts on all the vessels in the body in the same way that it does on those of the ear or mesentery, we first cut the vagi, sympathetics, and depressors; and then divide the spinal cord between the occiput and atlas, or atlas and axis, so as to sever the connexion between the vaso-motor centre and vessels, and begin artificial respiration. We next note the blood-pressure, inject the poison, and see what alterations it produces. Experiments may also be made by irritating the vagus or ligaturing the aorta.

ACTION OF SURROUNDING PARTS.—It sometimes happens, as in the case of physostigma, that the drug produces no contraction in the vessels of the ear or mesentery when their nerves are cut—a fact which shows that it acts on them through the vaso-motor nerves, and not directly on their walls; and nevertheless, when injected into a vein after the cord has been cut, it may cause the blood-pressure to rise very considerably. At first sight, this would seem to indicate that the drug acted on the walls of some vessels in the body, if not on those of the ear or mesentery, directly, and not through their vaso-motor nerves. On examination, however, it is found that the obstruction to the flow of blood through the capillaries does not depend on their contraction, but on the occlusion of a large number of them in the intestine by spasmodic contraction of the intestinal walls in which they are imbedded (101).

INFLUENCE OF THE PULMONARY CAPILLARIES.—It has lately been pointed out by Holmes (102) that when a drug such as ergot, which acts on the walls of the vessels and causes them to contract, is injected into the jugular vein, it has to pass through the pulmonary capillaries before it reaches the systemic ones; and, by contracting them, it will lessen the amount of blood sent into the aorta from the left ventricle, and will at first produce a fall in the arterial pressure, succeeded by a great rise when time has elapsed for the drug to reach the systemic capillaries and cause them likewise to contract.

USE OF THE SPHYGMOGRAPH.—For a description of the sphygmograph and the mode of applying it, we must refer to the special works on that subject, such as those of Marey and Sanderson. The indications which it gives are the following. 1. The greater or less pressure which is requisite to compress an artery and stop its pulsations enables us to estimate approximately the amount of pressure within it. The amount of pressure and the rapidity of the pulse help us to form conclusions regarding the motor and inhibitory apparatus of the heart, in the same way as in the experiments, already mentioned, though, of course, to a much more limited extent and with much less certainty. 3. The form of the curve, like those in Figs. 13 and 14, shows, in the same way as those of the sphygmoscope, Figs. 13 and 14, the rapidity with which the pressure falls during the diastole; and from this curve and the amount of blood-pressure we can judge of the size of the capillaries.

APPENDIX.

Artificial Circulation through Isolated Organs.—In order to study the effects of alterations in the blood, and the action of various poisons upon the walls of the vessels themselves, with entire exclusion of the nervous system, Ludwig and Mosso have kept up artificial circulation in the kidney and the liver. In removing these organs great care is taken not to wound them, and the diaphragm is removed along with the liver. In experimenting on the kidney large dogs were employed. The carotids were first opened, and blood allowed to flow until convulsions began. The artery was then closed for some time, during which the blood was defibrinated and part of it put into a flask, so as to be ready to wash out all the coagulable blood from the kidney. The carotids were now opened a second time, and as much blood as possible got from them by pressure on the abdomen, etc. As soon as the animal became insensible the abdomen was opened, the renal artery was then compressed just above its bification, so as to prevent any air getting into it, and a glass cannula was introduced into the main artery; another cannula was put into the renal vein. All the small vessels which communicate with adjacent parts were ligatured, and the kidney was then removed. Before connecting the cannula in the renal artery with the apparatus for artificial circulation, it was carefully filled by means of a fine pipette with defibrinated blood, and the utmost care employed to prevent any air bubbles from getting into the vessel. After the communication between the renal artery and the flask has been opened, it sometimes happens that blood does not flow until a considerable time has elapsed, owing apparently, to a tetanic contraction of the vessels in the kidney.

After the blood has begun to flow it does not do so in an equable stream, as it would do through glass tubes, but its velocity is alternately greater and less, owing to periodic contractions of the walls of the renal vessels, independently of any nervous influence. If the circulation is arrested for some time and then allowed to go on, the rapidity is much greater after than before the stoppage, but it gradually falls again to normal. Blood containing much carbonic acid and little oxygen (*erstickungsblut*), causes the vessels to contract, and the stream to become slow; while blood containing much oxygen and little carbonic acid causes them to dilate. When different sorts of blood are allowed to circulate after each other through the kidney, and each successive kind contains less CO_2 than the one preceding it, the rapidity of the flow from the vein goes on increasing; or, as it might be expressed, each kind of blood in this series seems to diminish the amount of contraction of the vascular walls which the greater amount of CO_2 in the preceding kind had occasioned. The order would be this—suffocation—blood—venous—arterial—apnœic, *i.e.*, saturated with oxygen, by agitation with air. This dilatation, however, was only temporary.

When nicotine was mixed with blood in the proportion of 1 to 10,000 it seemed, at first, to cause contraction of the vessels, for it produced a diminution in the flow of blood, and also in the size of the kidney; but both soon return to the normal. One per cent. of nicotine, on the contrary, seems to cause immediate dilatation of these vessels, for it immediately causes an increase in the velocity of the current and the size of the kidney. The increased velocity is not to be entirely ascribed to contraction of the vessels, for a solution of nicotine of this strength alters the blood, and will diminish the friction in the vessels.

Atropia has a powerful action, and different doses of it produce different effects. In the proportion of 1 in 100,000 it causes diminished rapidity in the flow of blood and in the volume of the kidney, but both soon return to their normal. One in 10,000 causes diminished, followed by increased rapidity, but this soon disappears. One in 5,000 soon kills the kidney, but before doing so causes first, diminution, and then acceleration of the current through it. Chloral hydrate first causes diminished and then greatly increased velocity, but it also has a very peculiar action on the vessels, increasing the rhythmical contractions in them when they are present, and causing them to appear when they were previously absent.

The shocks of an induction coil, or Faradaic currents, do not alter the velocity of the circulation, but constant currents do. During the time they are passing, both the rapidity of the current, and the size of the kidney increase, and after the irritation ceases they diminish. When the circulating blood contains a small quantity of chloral, this action is altered. At first, when the chloral has not altered the current much, it becomes slightly diminished during the irritation, and slightly increased after its removal. When the chloral has acted longer and increased the velocity of the current to five or six times its normal, no alteration is noticed during the application of the current, but a still further increase occurs after its removal.

After the kidney has been removed from the body for twenty-four hours, and kept in a cool place, its vessels still retain their irritability, but small doses of chloral in such a kidney only cause contraction, and larger doses of 0.3 to 0.5 per cent. are requisite to induce dilatation. The effect is not due to the action of the chloral on the blood, for it is produced when the blood is replaced by serum. One of the most extraordinary things about the action of chloral is that, in the dead kidney, instead of increasing the rapidity of the current, or leaving it unaltered, chloral greatly diminishes it—exactly the opposite to its effect on the living organ. When the blood used in the artificial circulation is saturated with carbonic acid chloral no longer produces any effect on the vessels, so its action would seem to be abolished by this gas.

Induction of Anæsthesia—At page 31 I have stated that chloroform is inadmissible as a narcotic, as its administration seemed to cause dogs so much pain, but farther experience has shown me that this statement is incorrect. Chloroform can be readily administered to all animals by placing them under a glass bell jar, along with a sponge or piece of blotting-paper, saturated with the anæsthetic. The advantage of the glass jar is, that the movements of the animals can be distinctly seen, and they can be removed immediately on their becoming insensible, thus avoiding the danger to which they would be exposed by longer inhalation of air saturated with the vapour. The vapour being heavier than air sinks to the bottom of the jar, and when the animal falls unconscious, the air it then respires is much more heavily charged with the vapour than that which it breathed while still erect. On account of the density of chloroform vapour, anæsthesia is more quickly produced when the bell jar has an opening at the top which can be plugged with cotton wool saturated with chloroform, than when the sponge is laid at the bottom of the jar; as in the former case the vapour falling down is more rapidly diffused through the air of the jar than in the latter. Instead of a bell jar a deep milk pan may be used, the rabbit or cat being placed in it, and the top covered by a towel stretched tightly over it. The chloroform is sprinkled on the towel. Anæsthesia is thus rapidly induced, but care must be taken not to allow the animal to remain too long in the vessel. For large dogs an inverted packing-case or box, without the lid, may be used instead of a bell jar.

After the animals have been rendered insensible and the operation has been begun, the anæsthesia may be kept up by putting a piece of cloth round the animal's nose and pouring chloroform upon it, a drop or two at a time, as often as is necessary. In this way less chloroform is required, and there is not so much danger of killing the animal by giving it the vapour in too concentrated a form.

Instead of keeping up the anæsthesia by the continued administration of chloroform, it is often more convenient to open a vein and inject opium or chloral.

In operations on the abdominal viscera in dogs, *e.g.*, in making gastric fistulæ, death sometimes occurs from shock, although the animals are completely under the influence of chloroform. For such operations ether is preferable, as it increases rather than diminishes the power of the heart. If given in the same way as chloroform, however, much time and a very large quantity of ether are required to produce anæsthesia. Professor Schiff has found, however, that it can be readily done by pouring a quantity of ether into a bladder, and holding this tightly around the dog's muzzle so that it respires ether vapour almost pure. As dogs do not like to be tied down, the muzzle shown at Fig. II, p. 28, should be put on, and the operator sitting on a low stool should put the dog's fore paws on his knee, and hold them with one hand, while with the other arm passed round the dog's body he restrains its movements, and an assistant holds the bladder with ether over the dog's nose.

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